

Janssen Research & Development *

Statistical Analysis Plan

A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis

**Protocol 54767414AMY3001; Phase 3
Amendment 2**

JNJ-54767414 (daratumumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

AE	Adverse event
AL amyloidosis	Light chain amyloidosis
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CHR	Complete hematologic response
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
C _{max}	Maximum observed concentration
C _{min}	Minimum observed concentration
CPR	Cardiac progression rate
CR	Complete response
CRF	Case report form
CRR	Cardiac response rate
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CyBorD	Cyclophosphamide, bortezomib and dexamethasone
dFLC	Difference between involved and uninvolved free light chains
DPS	Data presentation specification
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
FEV1	Forced Expiratory Volume in 1 second
FLC	Free light chain
HemPFS	Hematologic progression-free survival
HBV	Hepatitis B virus
IA	Interim analysis
IDMC	Independent Data Monitoring Committee
iFLC	Involved free light chain
IRC	Independent review committee
ITT	Intent-to-treat
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LLOQ	Lower limits of quantification
LPR	Liver progression rate
LRR	Liver response rate
MedDRA	Medical Dictionary for Regulatory Activities
M-protein	Monoclonal protein, monoclonal paraprotein
MOD	Major organ deterioration
MOD-PFS	Major organ deterioration-progression-free survival
MRD	Minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
NR	No response
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
ORR	Overall response rate
OrRR	Organ response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome
rHuPH20	Recombinant hyaluronidase PH20
RPR	Renal progression rate

RRR	Renal response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SF-36v2	36-Item Short Form Survey version 2
SOC	System organ class
SPEP	Serum protein electrophoresis
TEAEs	Treatment-emergent adverse events
TTOCP	Time to cardiac progression
TTOLP	Time to liver progression
TTORP	Time to renal progression
TNT	Time to next treatment
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
VGPR	Very good partial response
WBC	White blood cells

AMENDMENT HISTORY

SAP version	Issue Date
Original SAP	06Aug2018
Amendment 1	16Sep2019
Amendment 2	27Mar2020

This full study statistical analysis plan (SAP) has been revised. The rationale for the amendment and description of the changes are provided below.

Amendment -2**Rational for the amendment**

Based on FDA comments that dyspnea at rest for at least 3 consecutive days as a clinical manifestation of cardiac failure has subjective nature, it was requested to exclude from MOD-PFS definition. In addition, FDA has concern about patients who received subsequent treatment in the absence of hematologic progression or major organ deterioration

Summary of Changes:

- Dyspnea at rest for at least 3 consecutive days as a clinical manifestation of cardiac failure was excluded from MOD-PFS primary analysis
- The primary analysis of MOD-PFS will employ inverse probability of censoring weights (IPCW) method to adjust estimates of a treatment effect in the presence of subsequent non-cross resistant anti-plasma cell therapy.
- Added sensitivity analysis and supplementary analysis for MOD-PFS
- Added time to iFLC ≤ 20 mg/L response
- Minor edit changes for clarifications

Amendment -1 (16Sep2019)**Rationale for the amendment**

The primary endpoint, complete hematological response (CHR) rate and key secondary endpoints of major organ deterioration free survival (MOD-PFS) and overall survival (OS) remain the same. In the original plan, a progression-free survival (PFS) endpoint (defined as hematologic progression, or cardiac, kidney or liver progression, or death, whichever comes first) was planned. Considering that there is no literature currently available to assess for clinical meaningfulness of aggregate PFS as an endpoint in AL amyloidosis treatment, separate analyses will be conducted for hematological PFS and organ-based progression. In the revised plan, the PFS analysis will be specific to hematologic PFS (defined as hematologic progression, or death, whichever comes first). Additional landmark analysis on organ response and progression has been added for appropriate interpretation of results and meaningful comparison to existing literature. In addition, supportive analysis has been added as appropriate (e.g., analysis on iFLC and dFLC, time to PR or better and additional subgroups). Further editorial changes were made throughout the document for clarification.

Summary of changes:

- PFS analysis will be specific to hematologic PFS and moved to exploratory endpoint. PFS endpoint was removed from statistical hierarchical testing
 - Added organ response and progression 6-month landmark analysis for each involved organ
 - Added t(11:14) and high risk of cytogenetic subgroup
 - Added time to and duration of PR or better response
 - Added Time to iFLC<ULN and Time to dFLC<10 mg/dL response
 - Replaced time to organ progression with time to cardiac progression, time to renal progression and time to liver progression
 - Added attachments of hematologic PD and response computerized algorithm and additional exploratory analysis to support HEMAR.
 - Minor edit changes for clarifications
-

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the planned analyses for study JNJ-54767414AMY3001.

1.1. Trial Objectives

Primary Objective

The primary objective is to evaluate the efficacy of daratumumab plus CyBorD compared with CyBorD alone, in terms of overall complete hematologic response in the treatment of newly diagnosed AL amyloidosis patient.

Secondary Objectives

The secondary objectives are:

- To evaluate the clinically observable endpoints for major organ deterioration (MOD-PFS) following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To evaluate the following efficacy measures following treatment with daratumumab in combination with CyBorD compared with CyBorD alone:
 - Organ response rate (OrRR)
 - Overall survival (OS)
 - Time to and duration of response
- To evaluate fatigue, mental functioning, and health-related quality of life following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To assess the safety and tolerability of daratumumab when administered in combination with CyBorD
- To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPh20
- To explore minimal residual disease status in AL amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse

1.2. Trial Design

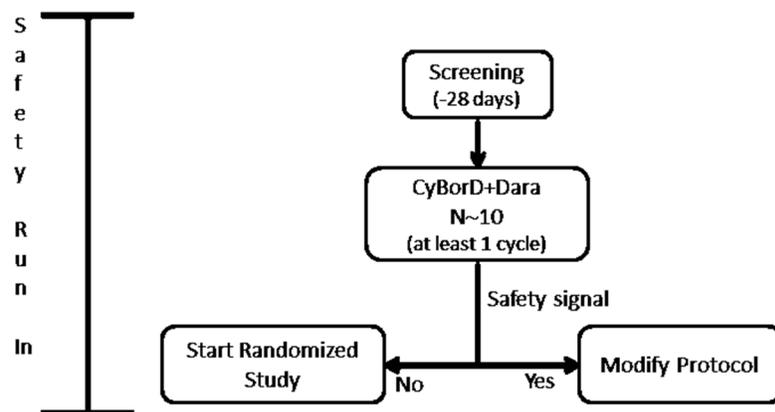
This is a randomized, open-label, active-controlled, multicenter Phase 3 study in subjects with newly diagnosed amyloid light chain amyloidosis. Approximately 360 subjects will be randomized in a 1:1 ratio to receive either CyBorD or CyBorD in combination with daratumumab (Dara SC+CyBorD). The randomization will be balanced by using randomly permuted blocks and will be stratified by cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥ 60 mL/min or CrCl < 60 mL/min).

Adult subjects age 18 and older with newly diagnosed AL amyloidosis are eligible for the study. Diagnosis will be based on histopathological or electron microscopy criteria, one or more organs need to be affected, and disease must be measurable (by serum monoclonal protein or free light chain criteria). Eligible subjects will have an ECOG performance score of 0, 1, or 2 and adequate

organ function as defined in the protocol. Key exclusion criteria include previous or current diagnosis of symptomatic multiple myeloma, evidence of significant cardiovascular conditions, any form of non-AL amyloidosis, or planned stem cell transplant during first 6 cycles of protocol therapy. Subject participation will include a Screening Phase, a Treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.

Given the potential safety concern with regards to the use of IV daratumumab in the AL amyloidosis population (ie, volume overload), this study will utilize the daratumumab SC co-formulation. Although the risk of volume overload is predicted to be lower with SC daratumumab than with IV infusion, patients with newly diagnosed AL amyloidosis may still develop adverse events attributable to hypervolemia (for example, dyspnea, peripheral edema, etc) secondary to amyloid-induced cardiac or renal insufficiency. Additionally, SC daratumumab has not been co-administered with CyBorD. Therefore, prior to the start of the randomized portion of the study, a safety run-in will be conducted (Figure 1). Dosing of these subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects have received at least 1 cycle of treatment. If no safety signal is observed, particularly in regard to volume overload, the randomized portion of the study will begin.

Figure 1: Schematic Overview of the Safety Run-In



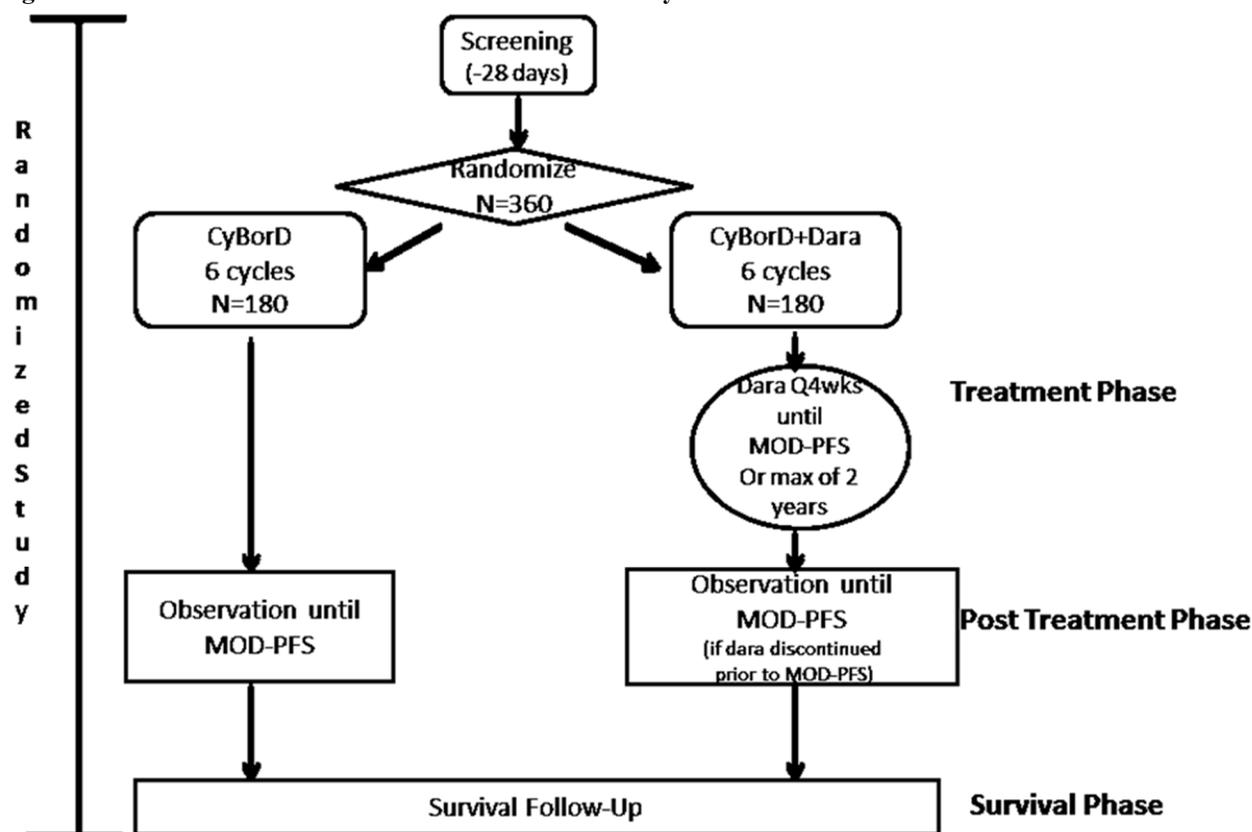
Subjects in the safety run-in will continue all scheduled assessments and contribute to the overall safety evaluation of the daratumumab in combination of CyBorD. However, these subjects will not be included in the overall efficacy assessment which will be based on the randomized subject population.

For subjects randomized to Dara SC+CyBorD, study drug (daratumumab) at fixed dose 1800 mg will be administered subcutaneously on weekly basis for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (Cycles 3-6), and then every 4 weeks until progression of disease or start of subsequent therapy, or a maximum of 2 years from the start of the study (Figure 2). For all daratumumab administrations, subjects will receive preinfusion medications to prevent infusion-related reactions. For the background (CyBorD) therapy, both treatment groups will receive up to 6 cycles (24 weeks) of CyBorD treatment.

Subjects will receive 300 mg/m² cyclophosphamide (maximum weekly dose 500 mg) as an oral or IV weekly dose and 1.3 mg/m² bortezomib as an SC injection weekly (Days 1, 8, 15, and 22) in every 28-day cycle for a maximum of 6 cycles.

Dexamethasone will be administered at a total dose of 40 mg weekly (ie, Days 1, 8, 15, 22). On days of daratumumab dosing, subjects in Dara SC+CyBorD will receive 20 mg on the day of daratumumab dosing as premedication and 20 mg on the day after daratumumab dosing. On weeks that daratumumab is not administered, or for subjects randomized to CyBorD, dexamethasone is to be given 40 mg weekly on a single day or divided into 2 days. For subjects who are older than 70 years, underweight (BMI <18.5), have hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/adverse event to steroid therapy, the dexamethasone dose may be administered at a dose of 20 mg weekly.

Figure 2: Schematic Overview of the Randomized Study



Throughout the study, evaluation of disease response and progression will be conducted in accordance with the consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis (Comenzo 2012)² and renal response and progression criteria by (Palladini 2014)³. In addition, recently published guidelines on response assessment will be taken into consideration when determining complete hematologic response (Manwani 2018, Muchtar 2019, Sidana 2019).^{6, 7, 10} A blinded Independent Review Committee (IRC) consisting of 3 experts in plasma cell disorders will evaluate and adjudicate responses.

Disease evaluations will be performed by a central laboratory (unless otherwise specified) according to the Time and Events Schedules until disease progression as defined by the MOD-PFS endpoint is documented, death, withdrawal of consent for study participation, or the end of study, whichever occurs first. Disease evaluations scheduled for study treatment days should be collected before study drug is administered. For free light chain assessment, M-protein, and immunofixation measurements in serum and 24-hour urine, the investigator will use results provided by the central laboratory. Subjects with positive serum IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for complete hematologic response (CHR), will be considered to be in a CHR.

Safety evaluations in this study will include adverse events, laboratory test results, electrocardiogram (ECGs), echocardiograms, vital sign measurement, physical examination findings and Eastern Cooperative Oncology Group (ECOG) performance status.

The primary endpoint of this study is overall complete hematologic response rate. The major secondary endpoints include MOD-PFS and OS. Analysis of the primary endpoint will be performed after all subjects have been treated for at least 6 cycles. The post-treatment phase will continue until 200 MOD-PFS events have been observed. The end of the study is defined to be 5 years after the last subject is randomized.

Two interim analyses are planned for this study. The first interim analysis is a pre-specified safety analysis and will occur after the first 30 subjects complete at least 1 cycle of treatment. The second interim analysis will be conducted for cumulative safety and efficacy and will occur after 180 subjects have been treated for at least 6 cycles. In addition to the 2 interim analyses, the IDMC will also review serious adverse event data at regular intervals during the study (i.e., after first interim analysis, and then approximately every 6 months).

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint is the overall complete hematologic response rate (CHR). The null hypothesis (H_0) is that there is no difference in overall CHR rate between Dara SC+CyBorD and CyBorD alone in subjects with newly diagnosed AL amyloidosis.

The null hypotheses (H_0) of no difference between the two treatment groups (Dara SC+ CyBorD and CyBorD) are evaluated for the following major secondary endpoints:

- MOD-PFS
- OS

These secondary hypotheses are to be tested in a sequential order as specified above. The details of the testing procedure are specified in Section [5.1.1](#).

1.4. Sample Size Justification

The sample size for this study is based on the alternative hypothesis of a 15% improvement in overall CHR rate. Taking an overall CHR rate estimated to be 25% for the CyBorD arm (Palladini 2015),⁴ adding a 15% improvement translates to an overall CHR rate of 40% for the Dara SC+CyBorD arm. Approximately 360 subjects (180 subjects per arm) would provide more than 85% power to detect a 15% improvement in overall CHR rate using a likelihood ratio test with a 2-sided alpha of 0.05.

The post-treatment observation phase will continue until 200 MOD-PFS events have been observed. Therefore, this study will achieve approximately 80% power to detect a 33% reduction in the risk of hematologic progression, major organ deterioration or death (hazard ratio [Dara SC +CyBorD vs. CyborD] of 0.67) with a log-rank test (2-sided alpha=0.05).

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared by vendor under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function ($\text{CrCl} \geq 60$ mL/min or $\text{CrCl} < 60$ mL/min). Country List A contains the countries that typically offer stem cell transplant while country List B contains the countries that do not offer stem cell transplant for patients with AL amyloidosis. After 6 cycles of study treatment, some subjects may receive stem cell transplant if recommended by the investigator. To minimize the imbalance in randomization among these patients, this country list variable is included as one of the stratification factors. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study treatment kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

As this is an open-label study, blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Study Part

In general, data collected in the study will be summarized and presented separately for Part 1 (safety run-in) and Part 2 (randomization). The start date for Part 1 is the date of the first study agent administration and the start date for Part 2 is date of randomization. In Part 1, limited analysis and summary tables such as subject disposition, demographic and baseline disease characteristics, disease response, and AE will be provided. For subjects randomized in Part 2, the data summaries and planned analyses are detailed in the rest of Sections of the SAP. Note that the analysis methods and definition rules applied in Part 2 analysis will be similarly applied to Part 1 analysis.

2.2. Visit Windows

For analyses of data by cycle, if data are collected by date (e.g., AE onset), the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study treatment administration data. The start date of a particular cycle is defined as the date of the first scheduled dose of any component of the study treatment, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last study treatment date plus 30 days or subsequent anticancer therapy minus 1 day, if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize data. However, due to possible cycle delays, assessment performed in the same cycle may not be well aligned in time scale for different subjects. To address this, by-week windowing rules may be applied in the overtime data summary by study week.

2.3. Pooling Algorithm for Analysis Centers

All participating centers in the study will be pooled together for analyses.

2.4. Study Treatment and Study Drug

In this study, study treatment refers to cyclophosphamide, bortezomib, dexamethasone, and daratumumab. Study drug refers to daratumumab.

2.5. Study Treatment Dosing Date

Study treatment dosing date is the date on which a subject actually received study treatment (partial or complete) and will be recorded in the study treatment administration dataset.

For subjects who receive Dara SC+CyBorD treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: bortezomib, cyclophosphamide, dexamethasone or daratumumab. The last study treatment date is defined as the latest date of non-zero dose of the following administration: bortezomib, cyclophosphamide, dexamethasone or daratumumab.

For subjects who receive CyBorD treatment, the first study treatment date is defined as the earliest date of non-zero dose of the following administration: bortezomib, cyclophosphamide, or dexamethasone. The last study treatment date is defined as the latest date of non-zero dose of the following administration: bortezomib, cyclophosphamide, or dexamethasone.

2.6. Treatment Cycle

A subject is considered as treated in a cycle if he/she receives any nonzero dose of bortezomib, cyclophosphamide, dexamethasone or daratumumab in that cycle.

2.7. Baseline Measurement

Baseline measurement is defined as the closest non-missing measurement taken on or prior to the first study treatment administration.

2.8. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters associated with disease assessment, the following rules will be applied to select the unique lab value for analysis: a) multiple records from both central and local lab, central lab value always takes precedence over local lab value; b) multiple records from central lab, select the latest value as the unique lab value; c) multiple records from local lab, select the latest lab value as the unique lab value.

2.9. Imputation of Partial Dates

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purpose, missing or partial date in adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), AL amyloidosis diagnosis (date of diagnosis), and subsequent anti-amyloidosis therapy (start date) data domain will be imputed.

2.9.1. Missing/Partial Adverse Event Onset Date

If the onset date of an adverse event is missing completely or partially, the following imputation rules will be used.

- When month and year are present and the day is missing,
 - If the onset month and year are the same as the month and year of first study treatment, the day of first study treatment or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier
 - If the onset month and year are not the same as the month and year of first study treatment, then the first day of the month is imputed
- When only a year is present or no components of the onset date are present,
 - If the onset year is the same as the year of first study treatment. If AE end date is available and is prior to first study treatment, the day and month of AE end date are imputed. Otherwise, the day and month of first study treatment are imputed
 - If the onset year is different from the year of first study treatment, the 1st of January is imputed
- If the onset date is completely missing, the date of first study treatment is imputed as the onset date.

No imputation will be done for partial or missing AE onset time.

If AE onset date needs imputation, but the AE onset time is available, the AE onset time will be dropped in the imputed AE onset date/time variable.

2.9.2. Missing/Partial Adverse Event End Date

If the end date of an adverse event is missing completely or partially, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.
- If the imputed date is later than the date of death (if available), the date of death will be used as the imputed date instead.

No imputation will be done for partial or missing AE end time.

If AE end date needs imputation, but the AE end time is available, the AE end time will be dropped in the imputed AE end date/time variable.

2.9.3. Partial Concomitant Medication Start/End Date

In case of partially missing concomitant medication start/end dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, the 15th day of the month will be used
- If both the day and month are missing, the 30th of June will be used

If the medication was taken prior to study start, and the imputed start date is after first treatment date, further adjust the imputed start date as the day prior to first dosing date; If the medication was taken after study start, and the imputed start date is prior to first dosing date, further adjust the imputed start date as first dosing date. Also adjust the imputed medication end date so that it is on or after first dosing date.

After applying above adjusting method, if it results in medication start date that is after medication end date, the medication start date needs re-adjustment as follows:

If medication start date was imputed, then adjust as follows:

- Impute the same month and year as medication end date if the non-imputed date parts are the same
- Impute the first day of the month as medication start day

If medication end date was imputed, then re-adjust medication end date to be the same as the medication start date if the corresponding non-imputed date parts match the medication start date.

Also adjust the imputed medication end date so that it is on or after first dosing date.

2.9.4. Partial AL Amyloidosis Diagnosis Date

For partial date of original AL amyloidosis diagnosis, the following imputation rules will apply:

- If only day is missing, the 15th day of the month will be imputed
- If both month and day are missing, the 30th of June will be imputed
- If year is missing, no imputation will be applied

If the imputed AL amyloidosis diagnosis date is after first treatment date, further adjust the imputed diagnosis date as the day prior to first dosing date.

2.9.5. Partial Subsequent Anti-AL Amyloidosis Therapy Start Date

If the year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day-component is missing, the following steps apply:

- If the month and year of the start date are the same as the month and year of last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.
- If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

No imputation will be applied for missing or partial subsequent anticancer therapy end date.

2.10. General Analysis Method

In general, continuous variables will be summarized using descriptive statistics (n, mean [SD] median, and range). Categorical variables will be summarized using frequency and percentage (n [%]). The Kaplan-Meier method will be used for descriptive summaries for time-to-event variables. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day will be used.

2.11. Analysis Sets

The following analysis sets are defined in this study.

2.11.1. Efficacy Analysis Set(s)

2.11.1.1. Primary Efficacy Analysis Set

The primary efficacy analysis set will be the intent-to-treat (ITT) population, which is defined as subjects who have been randomly assigned to the Dara SC+CyBorD or CyBorD arm. Analyses of the primary endpoint overall CHR rate, secondary endpoints, including time-to-event variables (e.g., MOD-PFS, and OS), and demographic and baseline characteristic etc. will be based on this population.

2.11.1.2. Secondary Efficacy Analysis Set

Secondary efficacy analysis sets are defined as follows:

- Hematologic response-evaluable: is defined as subjects who have a confirmed diagnosis of AL amyloidosis and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post- baseline disease assessment.

Supplementary analysis of CHR rate and VGPR or better rate will be based on this population. If >95% randomized subjects are hematologic response-evaluable, these supplementary analyses may be omitted.

- Cardiac response-evaluable is defined as subjects with baseline NT-proBNP value ≥ 650 ng/L or baseline NYHA class 3 or 4. In addition, subjects must have received at least 1 administration of study treatment and have at least one post-baseline NT-proBNP measurement (if baseline NT-proBNP ≥ 650 ng/L) or NYHA function evaluation (if baseline NYHA class 3 or 4)
- Renal response-evaluable is defined as subjects with baseline urine protein >0.5 g/day. In addition, subjects must have received at least 1 administration of study treatment and have at least one post-baseline urine protein (g/day) measurement
- Liver response-evaluable is defined as subjects with baseline abnormal alkaline phosphatase value (i.e., $>1.5 \times \text{ULN}$). In addition, subjects must have received at least 1 administration of study treatment and have at least one post-baseline alkaline phosphatase measurement

2.11.1.3. Safety Analysis Set

Safety analysis set is defined as subjects who have received at least 1 administration of any study treatment (partial or complete). This population will be used for all safety analyses. The safety analyses grouping will be according to treatment received.

2.11.1.4. Pharmacokinetics Analysis Set

Pharmacokinetics analysis set will be pharmacokinetics-evaluable population: is defined as subjects assigned to Dara SC+CyBorD arm who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion. All pharmacokinetics analyses are based on the pharmacokinetic evaluable population.

2.11.1.5. Immune Response-evaluable Analysis Set

Immune response-evaluable: is defined as subjects assigned to Dara SC+CyBorD arm who received at least 1 administration of daratumumab and had appropriate serum samples for detection of antibodies to daratumumab or rHuPH20 (i.e., subjects with at least 1 immunogenicity sample obtained after their first daratumumab administration). This analysis set will be used for immunogenicity related analyses.

2.12. Definition of Subgroups

In general, the following pre-specified subgroup (Table 1) analyses are to be performed for the primary efficacy endpoint, major secondary endpoints: MOD-PFS and OS, and safety endpoints. Additional subgroup analyses may be performed for selected efficacy and/or safety endpoints, which are described in later sections.

Table 1: Subgroup Analyses of Efficacy and Safety Endpoints

Subgroup	Definition	Analysis Type
Sex	Male, Female	E, S
Age	<65 years, ≥65 years	E, S
Race	White, Asian, Others	E, S
Baseline weight	≤ 65 kg, >65 to 85 kg, >85 kg	E, S
Baseline Cardiac stage	I, II, and IIIa/IIIb	E
Countries that typically offer transplant for patients with AL amyloidosis ^a	List A, List B	E
Baseline renal function (CrCl ≥60 mL/min or CrCl <60 mL/min))	≥60 mL/min; <60 mL/min	E, S
Cardiac involvement at baseline	Yes, No	E, S
Baseline Renal stage	I, II, III	E
Baseline Alkaline phosphatase ^b	Abnormal, normal	E
Achieve dFLC response ^c	Yes, No	E
t(11:14) by FISH	Abnormal, normal	E
High-risk	del 17p, t(4;14), t(14;16)	E
Baseline ECOG performance score	0, ≥1	E

^a List A = countries that typically offer transplant; List B = countries that typically not offer transplant.

^b Abnormal is defined as alkaline phosphatase value at baseline >1.5ULN.

^c dFLC response is defined as >50% reduction in the dFLC.

E: efficacy (CHR, MOD-PFS, OS); S: TEAE.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

Two interim analyses are planned for this study. The first interim will occur after the first 30 subjects are treated for at least 1 cycle in each arm. The purpose of the first interim analysis is to have a comprehensive evaluation of safety. The second interim analysis will occur after at least 180 subjects in total have been treated for at least 6 cycles. The purpose of the second interim analysis is to evaluate cumulative interim safety and efficacy data. Both futility and efficacy stopping rules are built in this interim analysis. The study may be stopped due to futility if the complete hematologic response rate in Dara SC+CyBorD arm is the same or worse than CyBorD arm. The study may be stopped due to efficacy if the significance level at this interim analysis to establish the superiority of Dara SC+CyBorD over CyBorD is less than or equal to 0.0001 (2-sided). The primary analysis will occur after all subjects are treated for at least 6 cycles and the alpha to be spent is 0.04999 (2-sided) by a user defined alpha spending function.

An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review the interim results at the planned interim analyses. After the interim review, the IDMC will make recommendations regarding any required modification and provide guidance on the continuation of the study. The details will be provided in a separate IDMC charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Unless specified otherwise, all demographic and baseline characteristics variables will be summarized for the ITT population. No statistical comparisons between the 2 treatment groups are planned.

The distribution of subject enrollment will be presented for each treatment group according to region and country. Subjects who did not meet study inclusion/exclusion criteria will be listed by subject ID, treatment group, and specific criteria not met.

Subject demographic and baseline characteristic variables: age, sex, ethnicity, race, weight (kg), height (cm), body surface area (m²), and ECOG performance status will be summarized by treatment group and overall.

Baseline amyloid disease characteristics will be summarized and tabulated by treatment group and overall. The baseline disease characteristics include time since initial AL amyloidosis diagnosis (months), type of AL amyloidosis (IgG, IgA, IgD, IgE, IgM, bioclonal) by immunofixation test, light chain type (kappa, lambda), type of measurable disease (serum M-protein, serum FLC, serum FLC + serum M-protein), t(11;14) by FISH (abnormal, normal), and standard-risk vs. high-risk cytogenetic abnormalities (del 17p, t(4;14), t(14;16)).

Baseline organ characteristics will also be summarized by treatment group and overall. Organ characteristics includes cardiac stage (I, II, IIIa/III_b) based on Mayo Cardiac Staging System, NYHA classification (I, II, IIIA), renal stage (I, II, III) and chronic kidney disease (CKD) stages based on published staging criteria (Palladini 2014)³, organ involvement (heart, kidney, liver, gastrointestinal track, lung, PNS, ANS, and soft tissue), and number of organ involvement (1, 2, ≥3 organs; median with range).

Disease related hematologic biomarkers (bone marrow plasma cell (%), iFLC and dFLC) at baseline will be summarized for all subjects, by descriptive statistics. Organ related biomarkers will be summarized for all subjects and subjects with specific organ involvement, respectively. These biomarkers include NT-proBNP, cardiac troponin T (cTnT), HS cardiac troponin T (Hs-cTnT), proteinuria, creatinine, eGFR, albumin, alkaline phosphatase, and LVEF, etc.

A descriptive summary of selected hematology (i.e, hemoglobin, neutrophils, platelet, and WBC) and chemistry (i.e., AST, ALT, alkaline phosphatase, total bilirubin, creatinine clearance, estimated glomerular filtration rate [eGFR]) laboratory analytes at baseline will be provided for each treatment group and overall. In addition, baseline toxicity grade of each selected laboratory analyte in hematology and chemistry panel will be summarized by treatment group using frequency.

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term for each treatment group and overall.

A summary of stratification factors (cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl \geq 60 mL/min or CrCl <60 mL/min) used in the randomization based on IWRS will be provided to evaluate if randomization process is appropriately executed in the study.

4.2. Disposition Information

An overview of subject disposition by treatment group will be provided. The overview includes a summary of total number of subjects who are randomized to each treatment group, the number and percentage of subjects who are randomized but not treated, and the number and percentage of subjects who are treated in each treatment group. For all treated subjects (defined as subjects who have received at least 1 administration of any study treatment), the number and percentage of subjects who discontinued study treatment including reason for discontinuation as indicated in the “Treatment Disposition” CRF page will be summarized.

According to study design, after a maximum of 6 cycles of CyBorD treatment, subjects who are assigned to Dara SC+CyBorD arm can continue to receive daratumumab monotherapy, if they have not progressed or received subsequent anti-plasma cell therapy. Therefore, to evaluate study treatment discontinuation during treatment period for both groups, the number and percentage of subjects who discontinued study treatment during Cycles 1-6 will also be provided.

Similar summaries will be presented for all randomized subjects who discontinued from study participation.

4.3. Extent of Exposure

Extent of exposure to study treatments will be summarized through the following variables: number of treatment cycles, duration of study treatment, total dose administered, dose intensity, relative dose intensity, and number of subjects with cycle delay and dose modification etc. These summaries will be based on safety analysis set and presented by treatment group.

The number and percentage of subjects treated within each cycle will be summarized. The maximum number of treatment cycles received for each subject will be summarized by frequency and descriptive statistics.

Duration of study treatment, defined as the number of days from the date of the first administration of study treatment to the date of the last administration of study treatment, will be summarized.

Number of Daratumumab injections and duration of 1st, 2nd and subsequent injections will be summarized.

Descriptive statistics for number of daratumumab administrations will be provided for Dara SC+CyBorD arm. The total dose administered for each study treatment (i.e. daratumumab [mg], cyclophosphamide [mg/m²], bortezomib [mg/m²], and dexamethasone [mg] or dex-equivalent if other steroid is used) will be summarized overall, by treatment cycle, by daratumumab treatment frequency (i.e. weekly [Cycles 1-2], biweekly [Cycles 3-6] and monthly [Cycles 7+]).

The dose intensity, which is defined as the sum of total dose administered in all cycles divided by the number of treatment cycles, will be calculated for each study treatment and summarized accordingly.

The relative dose intensity (%) defined as the ratio of total actual dose received and total planned dose will be calculated for each study drug and summarized using descriptive statistics.

The number of subjects with cycle delays or dose modifications (dose delays, dose skipping, or dose reduction) including reasons (AE or other) for cycle delays or dose modifications, will be reported. In addition, a summary of study treatment dose modifications by cycle will be provided.

4.4. Protocol Deviations

Major protocol deviations will be summarized based on ITT analysis set by the following types of deviation for each treatment group:

- Entered but did not satisfy inclusion/exclusion criteria
- Developed withdrawal criteria but not withdrawn
- Received wrong treatment or incorrect dose
- Received an excluded concomitant treatment
- Efficacy assessment deviation
- Other – protocol non-compliance

A listing of subjects with major protocol deviations including subject ID, type of deviation, and reasons for deviation will be provided.

Deviations specific to the COVID-19 pandemic will be presented by listing and narratives as appropriate.

4.5. Concomitant Medications

Concomitant medications collected beginning with signing of the ICF and ending 30 days after the last dose of the last study treatment or until the start of subsequent anticancer treatment, if earlier, will be summarized by therapeutic class, pharmacologic class, and drug name for each treatment group.

A similar summary of pre-infusion medication and post-infusion medication will be provided for Dara SC+CyBorD arm according to the CRF pages the medications are collected on.

In addition, systemic steroids and prophylactic antiviral medication use during the study will be tabulated by therapeutic class, pharmacologic class, and drug name, respectively.

4.6. Subsequent Non-cross Resistant Anti-plasma Cell Therapy for AL Amyloidosis

Non-cross resistant anti-plasma cell therapy for AL Amyloidosis is defined as any anti-plasma cell agent not included in the original protocol assigned treatment. For example, for subjects assigned to arm A who receives subsequent lenalidomide and bortezomib combination therapy, lenalidomide treatment will be considered as subsequent non-cross resistant, anti-plasma cell therapy. However, for subjects assigned to arm A who continues to receive cyclophosphamide, bortezomib and dexamethasone (CyBorD) or any component of cyclophosphamide, bortezomib and dexamethasone (e.g. bortezomib alone), subjects will not be considered as receiving subsequent, non-cross resistant, anti-plasma cell therapy.

Subsequent non-cross resistant anti-plasma cell therapy for AL Amyloidosis recorded during the study will be summarized and presented by therapeutic class, pharmacologic class and drug name for each treatment group. In AL amyloidosis disease setting, subsequent non-cross resistant, anti-plasma cell therapy could start earlier in some subjects prior to observation of hematologic progression, therefore, the summary will also be presented for a) subjects who initiated subsequent non-cross anti-plasma cell therapy prior to hematologic progression; b) subjects who initiated subsequent non-cross anti-plasma cell therapy on or after hematologic progression.

For subjects who received at least one line of subsequent non-cross anti-plasma cell therapy, the number of lines of subsequent therapy will be calculated for each subject and summarized by treatment group through frequency and descriptive statistics. In addition, their overall best hematologic and organ response to subsequent anti-plasma cell therapy will be summarized.

Additionally, hematologic and organ response to first subsequent non-cross resistant anti-plasma cell therapy will be tabulated. The reasons for initiation of first subsequent non-cross resistant anti-plasma cell therapy will be provided.

Please refer to Section 5.4.2 for analysis of time to non-cross resistant anti-plasma cell therapy for AL Amyloidosis.

5. EFFICACY

Evaluation of disease response and progression will be conducted in accordance with the “Consensus guidelines for the conduct and reporting of clinical trials in systemic light-chain amyloidosis (Comenzo 2012)”² and renal response and progression criteria by (Palladini 2014)³ (hereafter referred to as consensus guidelines). In addition, recently published guidelines on response assessment will be taken into consideration when determining complete hematologic response (Manwani 2018, Muchtar 2019, Sidana 2019).^{6, 7, 10}

The primary efficacy analysis will be conducted based on independent review committee (IRC) assessment of disease response and progression. Sensitivity analysis of hematologic response, which response and progression are evaluated by the sponsor using a computerized algorithm, will

be performed. The detailed documentation of the computer algorithm can be found in Attachment 1. Additionally, analysis will also be carried out for selected efficacy endpoints based on investigator assessment.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical hypothesis tests and 95% confidence interval presented will be 2-sided.

The primary hypothesis (i.e., hypothesis on overall CHR rate) is to be tested at the 0.05 significance level (overall). No alpha spending will be given at the first interim analysis, because the purpose of this interim analysis is to evaluate safety and no analysis will be performed for efficacy endpoints. The alpha to be spent at the second interim analysis (approximately 180 subjects are treated for at least 6 cycles), is 0.0001 (2-sided). If the observed two-sided p-value is smaller than this significance level, the superiority of Dara SC+CyBorD versus CyBorD with respect to overall CHR will be established, therefore, the primary hypothesis will not be re-tested at any subsequent timepoints. Otherwise, the primary hypothesis will be tested again at the planned primary analysis (after all subjects are treated for at least 6 cycles) with alpha to be spent is 0.04999 (2-sided) by a user defined alpha spending function.

By the time of second interim analysis, it is estimated that there will be a very limited number of events for major secondary endpoints of MOD-PFS and OS. Therefore, only descriptive analysis will be conducted without formal hypothesis testing. Formal hypothesis testing of these major secondary endpoints will be conducted at the planned primary analysis and/or when approximately 200 MOD-PFS events are observed according to group-sequential rules as defined in the following.

If the testing of the primary endpoint of overall CHR rate is statistically significant, the following major secondary endpoints ordered below will be sequentially tested at the planned primary analysis, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls Type I error rate. The major secondary endpoints are ordered as follows:

- 1) MOD-PFS
- 2) OS

The significance level at the planned primary analysis will be determined by the alpha-spending function specific to that endpoint. For MOD-PFS and OS endpoints, the O'Brien-Fleming alpha-spending function as implemented by the Lan-DeMets method will be used.

- For MOD-PFS, the exact information fraction at primary analysis is to be determined by the observed number of events divided by total planned MOD-PFS events. The exact significance level is to be determined per the O'Brien-Fleming alpha spending function.
- For OS, the information fraction at primary analysis is to be determined by the observed number of death events divided by total projected death events by the time of final OS

analysis. According to published data (Palladini, Blood 2015)⁴, 55% of subjects with newly diagnosed AL Amyloidosis treated with CyBorD were projected to survival 5 years. Assuming that Dara SC+CyBorD may reduce the risk of death (hazard ratio=0.75) by 25%, it is estimated that by the time of final OS analysis, approximately a total of 156 death events are projected to be observed.

If the null hypothesis for MOD-PFS endpoint fails to be rejected at the planned primary analysis, then OS will not be tested until the next analysis timepoint (e.g., MOD-PFS analysis). If the null hypothesis for MOD-PFS endpoint is rejected at the planned primary analysis, it will remain rejected and will not be re-tested at final OS analysis.

5.1.2. Independent Review Committee

Hematologic response and progression, organ response and progression will be adjudicated by an Independent Review Committee (IRC). Details of this part can be found in Attachment 4.

5.1.3. Data Handling Rules

There is no imputation planned for missing efficacy endpoints.

5.2. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the overall complete hematologic response (CHR) rate.

5.2.1. Definition

Complete hematologic response will be assessed by the independent review committee (IRC) and is based on consensus guidelines (Comenzo 2012)² and defined as negative serum and urine immunofixation, and normalization of FLC levels and FLC ratio.

During the conduct of this trial, it became apparent that there are limitations to the (Comenzo 2012)² guidelines based on deeper understanding of disease biology and outcomes (Manwani 2018, Muchtar 2019, Sidana 2019)^{6, 7, 10} that effect the definition of a complete hematologic response. CCI



The overall CHR rate is the proportion of subjects who achieve a CR confirmed by a subsequent assessment during or after the study treatment. Subjects with positive serum IFE and confirmed daratumumab IFE interference, that meet all other clinical criteria for CR will be considered CHR.

5.2.2. Estimand

The primary estimand for this study is defined by the following components:

- Treatment:

- Dara SC+CyBorD for up to 6 cycles followed by dara monotherapy until PD or start of subsequent non-cross resistant, anti-plasma cell therapy, or a maximum of 2 years from the start of the treatment
- CyBorD for up to 6 cycles followed by observation
- Population: subjects with newly diagnosed AL amyloidosis
- Endpoint: overall complete hematologic response (CHR)
- Intercurrent event:
 - Treatment discontinuation
 - Start of subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis without hematologic progression
- Measure of intervention: odds ratio of overall CHR rate

Two different strategies are used to account for the intercurrent events.

- Disease assessments after subsequent non-cross resistant, anti-plasma cell therapy will be ignored for a subject who started subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis (while on treatment strategy).
- Treatment discontinuation will be ignored (treatment policy strategy).

Note: please refer to Section 4.6 for the definition of non-cross resistant anti-plasma cell therapy for AL Amyloidosis.

5.2.3. Analysis Methods

The main analysis for the primary endpoint overall CHR rate will be based on IRC-assessed CHR.

Overall CHR rate will be calculated for each treatment group based on the ITT population. The corresponding 95% exact confidence interval (CI) will be provided. Stratified Cochran-Mantel-Haenszel (CMH) test will be used to test treatment difference in the proportion of subjects who achieved an overall CHR. The CMH estimate of odds ratio and its 95% CI and p-value for testing treatment difference will be reported. Stratification factors used in the analysis include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥ 60 mL/min or CrCl < 60 mL/min).

Subgroup analyses of CHR rate will be performed for pre-specified subgroups as described in Section 2.12.

A sensitivity analysis that target the primary estimand will be performed. The sensitivity analysis will be based on investigator assessed CR and computerized algorithm derived CR, respectively. Same analysis approach as for the main analysis will be implemented.

In addition, three planned supplementary analyses will be conducted. These are considered supplementary analyses as they inherently change the estimand. According to the ICH E9 addendum⁹ recommendations, only one component per analysis is changed at a time.

- a) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (i.e., negative serum and urine immunofixation and iFLC<ULN), the rest of the estimand remain the same
- b) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (i.e., negative serum and urine immunofixation and iFLC<ULN and normalization of FLC ratio), the rest of the estimand remain the same
- c) Changes which strategy is employed for the intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy. If there is a disease assessment that demonstrates CHR before PD after the start of subsequent non-cross resistant, anti-plasma cell therapy, the subject will be considered as a responder (treatment policy strategy)

5.3. Major Secondary Endpoints

The major secondary endpoints included in formal hierarchical hypothesis testing are MOD-PFS and OS. Other secondary endpoints include CHR at 6 months, hematologic VGPR or better rate, time to hematologic response, and duration of hematologic response. Except for time to and duration of hematologic response, analyses will be performed based on ITT set unless specified otherwise.

5.3.1. Major Organ Deterioration Progression-Free Survival (MOD-PFS)

5.3.1.1. Definition

MOD-PFS event is defined as one of the following clinically observable incidences:

- a) Death
- b) Major organ deterioration defined as
 - Clinical Manifestation of Cardiac Failure:
Defined as need for cardiac transplant, left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP)
 - Clinical Manifestation of Renal Failure:
Defined as the development of end-stage renal disease (need for hemodialysis or renal transplant)
- c) Development of hematologic PD as per consensus guidelines by IRC

MOD-PFS is defined as duration from the date of randomization to either hematologic progression, or major organ deterioration (clinical manifestation of cardiac failure or renal failure), or death, whichever occurs first.

5.3.1.2. Estimand

The estimand corresponding to the major secondary endpoint MOD-PFS for this study is defined by the following components:

- Treatment:
 - Dara SC+CyBorD for up to 6 cycles followed by dara monotherapy until PD or start of subsequent non-cross resistant, anti-plasma cell therapy, or a maximum of 2 years
 - CyBorD for up to 6 cycles followed by observation
- Population: subjects with newly diagnosed AL amyloidosis
- Endpoint: MOD-PFS
- Intercurrent event:
 - Treatment discontinuation
 - Start of subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis before hematological PD or major organ deterioration or death
- Measure of intervention: hazard ratio (HR)

Different strategies are used to account for the intercurrent events.

- Treatment discontinuation will be ignored (treatment policy strategy)
- For intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis before hematological PD or major organ deterioration or death, hypothetical strategy will be implemented. i.e., had subsequent, non-cross resistant, anti-plasma cell therapy not been available to subjects

Note: please refer to Section 4.6 for the definition of non-cross resistant anti-plasma cell therapy for AL Amyloidosis.

5.3.1.3. Analysis Methods

According to study design, a subject with suboptimal hematologic response or worsening organ function may switch to subsequent non-cross resistant, anti-plasma cell therapy before hematologic PD or major organ deterioration, which may impact or interfere with the evaluation of endpoint MOD-PFS. To adjust for confounding impact of subsequent, non-cross resistant anti-plasma cell therapy on MOD-PFS, the primary analysis of MOD-PFS will employ inverse probability of censoring weight (IPCW, Robins and Finkelstein, 2000)¹¹ method to adjust

estimates of a treatment effect in the presence of subsequent non-cross resistant, anti-plasma cell therapy.

5.3.1.3.1. Censoring Rules for MOD-PFS

Subjects who received subsequent non-cross resistant, anti-plasma cell therapy before hematological PD or major organ deterioration or death will be censored at the last disease assessment before start of subsequent non-cross resistant, anti-plasma cell therapy.

Subjects who withdraw consent from the study before MOD-PFS event will be censored at the last disease assessment before withdrawal of consent to study.

Subjects who are lost to follow-up before MOD PFS event will be censored at the last disease assessment before subjects are lost to follow-up.

Subjects who don't experience MOD-PFS event and are still alive at the cutoff date for analysis will be censored at the last disease assessment.

Subjects without any post-baseline disease assessment will be censored at randomization.

Determination of dates of MOD-PFS event and dates for censoring is summarized in Table 2 as follows.

Table 2: MOD-PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Hematologic PD or clinical manifestation of cardiac failure or clinical manifestation of renal failure prior to start of subsequent, non-cross resistant, anti-plasma cell therapy	Earliest date of any of these 3 events	MOD-PFS event
Death prior to start of subsequent, non-cross resistant, anti-plasma cell therapy	Date of death	MOD-PFS event
No post-baseline clinical evaluation of MOD-PFS	Randomization	Censored
No MOD-PFS events	Date of last clinical evaluation of MOD-PFS endpoint	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent, non-cross resistant, anti-plasma cell therapy etc.)	Date of last clinical evaluation of MOD-PFS endpoint prior to censoring situation	Censored

5.3.1.3.2. Inverse Probability of Censoring Weighted (IPCW) Analysis

The primary analysis of MOD-PFS will be based on IRC event assessment for the ITT population.

The number and percentage of subjects who have a MOD-PFS event or are censored including reasons for censoring will be reported. The detailed breakdown of events by each component (hematologic PD, major organ deterioration or death) will also be provided.

The primary treatment comparison of the distribution of overall MOD-PFS will be based on inverse probability of censoring weighted (IPCW, Robins and Finkelstein, 2000)¹¹ log-rank test to adjust for potential dependent censoring due to switching to subsequent non-cross resistant, anti-plasma cell therapy. Due to expected small number of MOD-PFS events at the primary analysis, the distribution comparison of MOD-PFS for the 2 treatment groups will be based on unstratified IPCW log-rank test (i.e. score test from unstratified IPCW weighted cox-proportional hazard model). The p-value from the unstratified IPCW log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated using a unstratified weighted Cox proportional hazards model with treatment as the sole explanatory variable. Inverse probability of censoring weighted Kaplan-Meier curves will be plotted by treatment group. At the final MOD-PFS analysis (i.e., when approximately 200 MOD-PFS events have been observed), a stratified MOD-PFS analysis including stratified IPCW log-rank test, stratified weighted Cox proportional hazards model with treatment as the sole explanatory variable will be performed.

Time-dependent stabilized weights will be calculated for each subject at time (t) by estimating the conditional probability of having remained uncensored (i.e., not switching to subsequent non-cross resistant, anti-plasma cell therapy) until time t given baseline covariates, divided by the estimated conditional probability of having remained uncensored until time t given baseline and time-dependent covariates.

The conditional probability of the subject having remained uncensored (i.e., not switching to subsequent non-cross resistant, anti-plasma cell therapy) until time t will be estimated based on the treatment specific fits of a Cox proportional hazards model for switching to subsequent non-cross resistant, anti-plasma cell therapy. Subjects who receive subsequent non-cross resistant, anti-plasma cell therapy without experiencing a MOD-PFS event or before experiencing a MOD-PFS event will be considered as an event for treatment switching, with event date as the start date of subsequent non-cross resistant anti-plasma cell therapy; Subjects who receive subsequent non-cross resistant, anti-plasma cell therapy after experiencing a MOD-PFS event will be censored at time of the MOD-PFS event. Subjects who don't receive subsequent non-cross resistant, anti-plasma cell therapy at the cutoff date for analysis will be censored at the last disease assessment.

The following baseline covariates and time-dependent prognostic factors for MOD-PFS and switching to subsequent non-cross resistant, anti-plasma cell therapy will be taken into consideration.

Baseline covariates	<ul style="list-style-type: none"> • Age (<65, >=65) • Sex (Male, Female) • Race (White, Others) • ECOG Performance Score (0, >=1) • Countries that typically offer transplant for patients with AL amyloidosis (List A: countries that typically offer transplant or List B: countries that typically not offer transplant) • Baseline dFLC
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	<ul style="list-style-type: none"> • Baseline iFLC • Type of FLC (kappa, lambda) • Number of organ involvement (<2, vs >=2) • Cardiac involvement (Y, N) • Cardiac stage (Stage I, II, and III_a/III_b), • Renal involvement (Y, N) • Renal function (CrCl ≥60 mL/min or CrCl <60 mL/min) • Renal Stage (I, II, III)
Time varying covariates	<ul style="list-style-type: none"> • dFLC • iFLC level • PR status • CR status • Worsening in hematologic response criterion from best achieved status • Alkaline Phosphate • eGFR • Proteinuria level • NT-proBNP • Progression of organ disease (Heart, Kidney and Liver) as defined in protocol Table 10 by laboratory values • Organ response (Heart, Kidney and Liver) as defined in protocol Table 10 by laboratory values • Interaction of organ function (protocol Table 10) and hematologic response (PR or better) • Interaction of organ function (protocol Table 10), hematologic response (PR or better) and treatment cycle (<=6 vs >6). • Exposure to study treatment (study drug discontinued or not)

Variable selection methods will be used to increase modelling stability and to restrict the number of covariates and time-dependent prognostic factors in the model to the ones that best fit both MOD-PFS data and switching to subsequent non-cross resistant, anti-plasma cell therapy based on stratified Cox proportional hazard model with treatment group as the only stratification factor.

Transformations to continuous lab variables will be implemented where necessary, to increase stability of the modelling approach (e.g. log-transformation for dFLC and iFLC values and (baseline) adjustments for individual effects). Missing time-varying covariate observations will be imputed by the last available assessment prior to missingness.

Any missing conditional probabilities (numerator / denominator) in the calculation of weights will be set to 1. To increase stability of the final IPCW weights, these will be truncated to the 2.5% and 97.5% quantile of the calculated weights.

The robustness and impact of the variable selection, modelling and weighting approach on the estimates will be evaluated by means of sensitivity IPCW analysis, including:

- Inclusion of all covariates and time-dependent prognostic factors into the calculation of weights.
- Calculation of weights without applying stabilizing transformations to time-varying prognostic factors.
- Calculation of weights using logistic regression for modelling time to initiation of subsequent non-cross resistant, anti-plasma cell therapy.

5.3.1.4. Sensitivity Analysis of MOD-PFS

Three planned sensitivity analyses that target the estimand for MOD-PFS will be performed.

- a. MOD-PFS based on investigator assessed hematologic PD. Same analysis approach as for the primary analysis (IPCW method) will be implemented
- b. MOD-PFS based on IRC assessment by using naïve censoring method (i.e., censoring subjects at the last disease assessment before start of subsequent non-cross resistant, anti-plasma cell therapy)

Stratified log-rank test and stratified Cox's regression model with treatment as the sole explanatory variable will be used to estimate treatment effect (i.e. hazard ratio and its 95% confidence interval)

- c. Unstratified analysis of MOD-PFS based on IRC assessment by using naïve censoring method

Log-rank test and Cox's regression model with treatment as the sole explanatory variable will be used to estimate treatment effect (i.e. hazard ratio and 95% CI)

5.3.1.5. Supplementary Analysis of MOD-PFS

Supplementary analyses including other strategies for intercurrent events of subsequent non-cross resistant, anti-plasma cell therapy such as treatment policy strategy (no censoring at start subsequent non-cross resistant, anti-plasma cell therapy) and composite strategy (subsequent non-cross resistant, anti-plasma cell therapy will be treated as a MOD-PFS event) will be performed.

5.3.1.5.1. Ignore Subsequent Non-Cross Resistant Anti-Plasma Cell Therapy

The MOD-PFS defined in Section 5.3.1.1 will be analyzed by using treatment policy strategy to handle intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy, in other

words, if a subject receives subsequent non-cross, anti-plasma cell therapy prior to hematologic progression or major organ deterioration, the subject will not be censored at the last disease assessment before start of subsequent non-cross, anti-plasma cell therapy.

The primary treatment comparison of the distribution of overall MOD-PFS will be based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function ($\text{CrCl} \geq 60 \text{ mL/min}$ or $\text{CrCl} < 60 \text{ mL/min}$).

5.3.1.5.2. MOD-Event Free Survival (MOD-EFS)

MOD-EFS is a supplementary analysis to MOD-PFS by implementing composite strategy to the intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis.

MOD-EFS is defined as hematologic PD, major organ deterioration, initiation of any subsequent non-cross resistant, anti-plasma cell therapy, or death, whichever comes first.

The primary treatment comparison of the distribution of overall MOD-EFS will be based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function ($\text{CrCl} \geq 60 \text{ mL/min}$ or $\text{CrCl} < 60 \text{ mL/min}$).

Additionally, MOD-EFS analysis based on IRC assessed subsequent non-cross resistant, anti-plasma cell therapy event will be performed.

5.3.1.5.3. Subsequent Non-Cross Resistant Anti-Plasma Cell Therapy as a Time Dependent Covariate

A time-dependent Cox proportional-hazards model with subsequent non-cross resistant, anti-plasma cell therapy as a time dependent covariate will be performed for MOD-PFS.

This time dependent Cox proportional-hazards regression model included three variables:

1. Treatment group,
2. A time dependent covariate (an indicator function for each subject, taking the value of 0 from randomization to start of subsequent non-cross resistant, anti-plasma cell therapy, and 1 thereafter), and
3. The interaction term of the above 2 variables.

This analysis will evaluate treatment effect before and after any subsequent non-cross resistant, anti-plasma cell therapy.

5.3.1.5.4. Censored for Death/PD after Missing More Than One Disease Evaluation

A supplementary analysis of MOD-PFS based on computer algorithm by censoring for death or hematologic progression after missing more than one consecutive disease evaluation will be performed in a similar manner as described in Section 5.3.1.5.1.

The MOD-PFS definition used in the supplementary analysis is similar to that defined in Section 5.3.1.1, except for death or hematologic progression after missing more than one consecutive disease evaluation. For any MOD-PFS (death or hematologic progression) event, if the event date and the latest date of scheduled disease evaluation (includes serum M-protein, urine M-protein, and serum FLC) immediately preceding the event differs more than 2.5 cycles, which indicates that subject missed at least one scheduled disease evaluation, then this event will not be considered as a MOD-PFS event in the supplementary analysis. Instead, the subject will be censored at the date of last disease evaluation (includes serum M-protein, urine M-protein, and serum FLC) prior to the MOD-PFS event originally identified.

Note that for subjects with missing disease assessments due to impact of COVID-19, the window rules may be adjusted, accordingly.

5.3.1.5.5. Exclude Hematologic Progression From MOD-PFS Definition

A supplementary analysis of MOD-PFS with adjusted MOD-PFS definition excluding hematologic progression from MOD-PFS will be performed in the same manner as described in Section 5.3.1.5.1.

In addition to analysis described in Section 5.3.1, a 6-month landmark analysis may be conducted to explore the correlation between MOD-PFS and CHR at 6 months. The Kaplan-Meier MOD-PFS curve will be plotted by hematologic response.

5.3.2. Overall Survival (OS)

5.3.2.1. Definition

Overall survival (OS) is measured from the date of randomization to the date of the subject's death. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

5.3.2.2. Analysis Methods

OS will be analyzed for the ITT population. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Median OS with 95% CI will be provided. In addition, the number and percentage of subjects who had died or were censored will be reported. The Kaplan-Meier OS curve will also be plotted by treatment group.

Due to expected small number of death events at the planned final analysis, the distribution of OS for the 2 treatment groups will be compared based on an unstratified log-rank test. A p-value from an unstratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on an unstratified Cox's regression model with treatment as the sole explanatory variable.

A summary of reasons for censoring of overall survival will be provided.

At the final OS analysis, a stratified OS analysis will be performed. Stratification factors that are used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function ($\text{CrCl} \geq 60 \text{ mL/min}$ or $\text{CrCl} < 60 \text{ mL/min}$). In addition, 4 and 5-year survival rates will be reported.

As described in Section 5.3.1.3, subsequent non-cross resistant, anti-plasma cell therapy are permitted to start before hematologic progression in this disease setting. A large number of subjects who receive subsequent anti-plasma cell therapy may confound the analysis of overall survival. At the final OS analysis, exploratory analysis may be performed that adjust for the effect of treatment switch on overall survival.

A 6-months landmark analysis may be conducted to explore the correlation between OS and CHR at 6 months. The Kaplan-Meier OS curve will be plotted by hematologic response.

5.3.3. Complete Hematologic Response Rate at 6 Months

5.3.3.1. Definition

CHR rate at 6 months is defined as the proportion of subjects who achieve a complete hematologic response at 6 months (i.e., initial or confirmation is within 6 +/- 1 months).

5.3.3.2. Analysis Methods

The primary analysis for CHR rate at 6 months will be based on IRC-assessed CHR. A sensitivity analysis of CHR rate at 6 months based on investigator assessment and computerized algorithm will be performed to evaluate the robustness of CHR rate at 6 months. In addition, CHR without confirmation rules applied by the computerized algorithm will also be explored.

Analysis of CHR rate at 6 months will be performed similarly as the primary endpoint CHR rate. In addition, CHR rate at 12 months and 18 months may be provided.

5.3.4. Hematologic VGPR or better Rate

5.3.4.1. Definition

Hematologic VGPR or better rate is defined as the proportion of subjects who achieve confirmed a hematologic CR or VGPR.

5.3.4.2. Analysis Methods

The primary analysis for hematologic VGPR or better rate will be based on IRC-assessed response. Hematologic response assessed by investigator will be used as supportive evidence.

Hematologic VGPR or better rate will be analyzed similarly as the primary endpoint CHR rate.

5.3.5. Time to Hematologic Response

5.3.5.1. Definition

Time to hematologic response analysis will be based on IRC-assessed response, the analysis includes time to CHR, time to VGPR or better and time to PR or better response.

- Time to CHR is defined as the time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for hematologic CR.
- Time to hematologic VGPR or better is defined as the time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for hematologic VGPR or CR.
- Time to hematologic PR or better response is defined as the time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for hematologic PR or VGPR or CR.

5.3.5.2. Analysis Methods

For subjects who achieve a hematologic CR, descriptive statistics will be provided to summarize time to CHR.

The similar analysis will be performed for subjects who achieve a hematologic VGPR or better or hematologic PR or better response.

5.3.6. Duration of Hematologic Response

5.3.6.1. Definition

Duration of hematologic response analysis will be based on IRC assessed response, the analysis includes duration of CHR, duration of VGPR or better response and duration of PR or better response.

- Duration of CHR is defined for subjects with CHR as the time from the date of initial documentation of CHR to the date of first documented evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.
- Duration of hematologic VGPR or better is defined for subjects with hematologic VGPR or better as the time from the date of initial documentation of hematologic VGPR or better to the date of first documented evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.
- Duration of hematologic PR or better response is defined as the time from the date of initial documentation of hematologic PR or VGPR or CR to the date of first documented

evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.

5.3.6.2. Analysis Methods

For subjects who achieve a hematologic CR, median duration of CHR with 95% CI will be estimated based on the Kaplan-Meier method for each treatment group. The Kaplan-Meier curves will be plotted by treatment group.

No formal statistical comparison of duration of CHR between the treatment groups will be made.

The similar analysis will be performed for subjects who achieve a hematologic VGPR or better or hematologic PR or better response.

5.4. Other Efficacy Endpoints

5.4.1. Hematologic PFS (HemPFS)

5.4.1.1. Definition

Hematologic PFS is defined as the time from the date of randomization to the date of hematologic progression assessed by IRC, or death due to any cause, whichever occurs first. Subjects who withdraw consent from the study before hematologic progression will be censored at the last hematologic assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last hematologic assessment before subjects are lost to follow-up. Subjects who don't have a HemPFS event and are still alive at the cutoff date for analysis will be censored at the last hematologic assessment. Subjects without any post-baseline hematologic assessment will be censored at randomization.

Determination of dates of hematologic PFS event and dates for censoring is summarized in [Table 3](#) as follows.

Table 3: Hematologic PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Hematologic PD per consensus guidelines	Earliest date of progression	HemPFS event
Death	Date of death	HemPFS event
No post-baseline hematologic disease assessment	Randomization	Censored
No hematologic PFS events	Date of last clinical evaluation hematologic disease assessment	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up etc.)	Date of last clinical evaluation hematologic disease assessment	Censored

According to study design, for subjects with suboptimal hematologic response or worsening organ function, subsequent non-cross resistant, anti-plasma cell therapy for AL amyloidosis are permitted to start before hematologic progression in this disease setting, to evaluate overall

treatment effect, the hematologic PFS will not be censored at the starting of subsequent non-cross resistant, anti-plasma cell therapy.

5.4.1.2. Analysis Methods

Analysis of HemPFS will be based on IRC assessment for the ITT population. The Kaplan-Meier method will be used to estimate the distribution of overall HemPFS for each treatment group. The median HemPFS with 95% CI will be provided. In addition, the number and percentage of subjects who had a HemPFS event or were censored will be reported. The Kaplan-Meier PFS curve will also be plotted by treatment group.

The primary treatment comparison of the distribution of overall HemPFS will be based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function ($\text{CrCl} \geq 60 \text{ mL/min}$ or $\text{CrCl} < 60 \text{ mL/min}$).

Sensitivity analysis of HemPFS based on investigator assessment will be performed in a similar manner.

5.4.2. Time to Subsequent Non-cross Resistant Anti-plasma Cell Therapy

5.4.2.1. Definition

Time to subsequent non-cross resistant, anti-plasma cell therapy is defined as the time from the date of randomization to the start date of subsequent non-cross resistant, anti-plasma cell therapy. Death due to PD without start of subsequent non-cross resistant, anti-plasma cell therapy will be considered as an event. Subjects who withdraw consent to study or are lost to follow-up or die due to causes other than disease progression will be censored at the date of death or the last date known to be alive.

5.4.2.2. Analysis Methods

The Kaplan-Meier method will be used to estimate the distribution of time to subsequent non-cross resistant, anti-plasma cell therapy for the ITT population. Median time to subsequent non-cross resistant, anti-plasma cell therapy with 95% CI will be tabulated for each treatment group. In addition, a Kaplan-Meier curve for time to subsequent non-cross resistant, anti-plasma cell therapy will be plotted. The hazards ratio and its 95% CI will be obtained through a stratified Cox's regression model with treatment as the sole explanatory variable. Treatment comparison will be made via a stratified log-rank test.

5.4.3. Time to iFLC<ULN, iFLC \leq 20 mg/L and Time to dFLC<10 mg/L Response

5.4.3.1. Definition

Time to iFLC<ULN response is defined as the time from the date of randomization to the date of the first disease evaluation that subject's iFLC level reduction to less than ULN, confirmed by a subsequent assessment.

Time to iFLC \leq 20 mg/L response is defined as the time from the date of randomization to the date of the first disease evaluation that subject's iFLC level reduction to less than or equal to 20 mg/L, confirmed by a subsequent assessment.

Time to dFLC<10 mg /dL ("stringent dFLC response") response is defined as the time from the date of randomization to date of the first disease evaluation that subject's dFLC level reduction to less than 10 mg/dL, confirmed by a subsequent assessment.

5.4.3.2. Analysis Method

For subjects who achieve iFLC<ULN, iFLC \leq 20 mg/L or dFLC<10 mg/L ("stringent dFLC response) response, descriptive statistics will be provided to summarize time to iFLC<ULN, iFLC \leq 20 mg/L and time to dFLC<10 mg/L, respectively.

5.4.4. Organ Response

Organ response analysis will focus on individual organ involved at baseline, specifically for heart, kidney and liver. Organ response is defined using consensus guideline (refer to Section 5 of the SAP) and organ response requires confirmation by a subsequent assessment.

5.4.4.1. Cardiac/Renal/Liver Response Rate at 6 Months

5.4.4.1.1. Definition

Cardiac response rate (CRR) at 6 months is defined as the proportions of cardiac response-evaluable subjects (defined in Section 2.10 of the SAP) who achieved cardiac response at 6 months (i.e., initial or confirmation is within 6 +/- 1 months).

Similarly, renal response rate (RRR) and liver response rate (LRR) at 6 months will be defined in the same manner.

5.4.4.1.2. Analysis Methods

CRR at 6 months will be calculated for each treatment group based on the cardiac response-evaluable population. The corresponding 95% exact CI will be provided.

Stratified Cochran-Mantel-Haenszel (CMH) test will be used to test treatment difference in the proportion of subjects who achieved cardiac response at 6 months. The CMH estimate of odds ratio and its 95% CI and p-value for testing treatment difference will be reported. Stratification factors used in the analysis include cardiac stage (Stage I, II, and IIIa), countries that typically

offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl \geq 60 mL/min or CrCl <60 mL/min).

The similar analysis will be performed for RRR at 6 months and LRR at 6 months. In addition, CRR, RRR and LRR at 12 months and 18 months may be provided.

Additionally, a total number of subjects who achieve overall organ response during the study will be reported for each specific organ.

5.4.4.2. Time to Cardiac/Renal/Liver Response

5.4.4.2.1. Definition

Time to cardiac response is defined as the time between the date of randomization and the first efficacy evaluation at which the subject has cardiac response.

A similar definition will be defined for time to renal and time to liver response.

5.4.4.2.2. Analysis Methods

For subjects who are in cardiac response-evaluable population and achieve a cardiac response, descriptive statistics will be provided to summarize time to cardiac response.

A similar analysis will be performed on time to renal response and time to liver response, if applicable.

5.4.5. Organ Progression

Organ progression analysis will focus on each organ involved at baseline, specifically for heart, kidney and liver. Organ progression is defined using consensus guideline (refer to Section 5 of the SAP). A transient increase in NT-proBNP, and AP or transient decrease in eGFR meeting organ progression criteria are not considered for organ progression if this persisted <6 months and levels returned to baseline level or better.⁸

5.4.5.1. Cardiac/Renal/Liver Progression Rate at 6 Months

5.4.5.1.1. Definition

Cardiac progression rate (CPR) at 6 months is defined as the proportions of cardiac response-evaluable subjects (defined in Section 2.10 of the SAP) who experienced cardiac progression at 6 months (i.e., initial or confirmation is within 6 +/- 1 months).

Renal progression rate (RPR) and liver progression rate (LPR) at 6 months will be defined in a similar fashion.

5.4.5.1.2. Analysis Methods

CPR at 6 months will be calculated for each treatment group based on the cardiac response-evaluable population. The corresponding 95% exact CI will be provided.

The similar analysis will be performed for RPR and LPR at 6 months.

5.4.6. Time to Cardiac/Renal/Liver Progression

5.4.6.1. Definition

Time to cardiac progression (TTOCP) is defined as the time from the date of randomization to the date of cardiac progression. Subjects who withdraw consent from the study before cardiac progression will be censored at the last cardiac assessment before withdrawal of consent to study. Subjects who are lost to follow-up will be censored at the last cardiac assessment before subjects are lost to follow-up. Subjects who don't have cardiac progression and are still alive at the cutoff date for analysis will be censored at the last cardiac assessment. Subjects without any post-baseline cardiac assessment will be censored at randomization.

Time to renal progression (TTORP) and time to liver progression (TTOLP) will be defined in a similar manner as time to cardiac progression.

Determination of dates of time to cardiac/renal/liver progression event and dates for censoring is summarized in [Table 4](#) as follows.

Table 4: Time to Cardiac/Renal/Liver Progression Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Cardiac/renal/liver PD per consensus guidelines	Earliest date of progression	event
No post-baseline organ disease assessment	Randomization	Censored
No events	Date of last clinical evaluation of organ disease assessment	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up etc.)	Date of last clinical evaluation of organ disease assessment	Censored

5.4.6.2. Analysis Methods

5.4.6.3. Analysis Methods

Analysis of TTOCP will be based on the cardiac-evaluable population. The Kaplan-Meier method will be used to estimate the distribution of overall TTOCP for each treatment group. The median TTOCP with 95% CI will be provided. The Kaplan-Meier PFS curve will also be plotted by treatment group.

Analysis of time to renal and liver progression will be performed in a similar manner.

5.5. Patient-Reported-Outcome (PRO)

Patient-reported-outcome (PRO) will be evaluated in this study through the following 3 instruments: EORTC QLQ-C30 with 4 supplemental questions from the EORTC item bank, EQ-5D-5L and SF-36. Scoring for each instrument will be done based on the instrument developer guidelines. No imputation will be done for the PRO data.

On the days that PROs are scheduled, the PROs should be administered before any other study procedures. If a subject has completed the PRO assessments and dosing is delayed, the PRO assessment does not need to be repeated if the assessment occurs ≤ 4 days before dosing.

5.5.1. Definition

The EORTC QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week (the past week). A higher score represents a higher (“better”) level of functioning, or a higher (“worse”) level of symptoms.

The EQ-5D-5L is a generic measure of health status. For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effectiveness analyses. The EQ-5D-5L is a 5 item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating “health today” with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual (but scoring by the UK algorithm allows for values less than 0).

The SF-36 Health Survey is a generic measure of health status. The SF-36 consists of 36 questions that yield an eight-scale (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) profile of functional health and well-being, as well as 2 physical and mental health summary measures and a preference-based health utility index. The physical component summary (PCS), the mental component summary (MCS), and the 8 domain scores range from zero (0) to 100, with higher scores representing higher level of functioning.

5.5.2. Analysis Methods

Analysis of PRO data will be performed on ITT analysis set. For subjects with multiple records at the same visit, the closest one to the visit date will be selected as the scheduled assessment.

At each time point for analysis, the number and percentage of PRO instrument assessment forms that are expected, received and missing will be tabulated by treatment group. The missing PRO assessments are defined as the expected number of assessments for a visit minus the actual number of assessments received for that visit, the expected number of assessments per visit will be determined by subject-level study completion status.

Key PRO endpoints

The PRO endpoints are secondary and not part of the statistical hierarchy. Type 1 error control will not be applied to PRO data.

- EORTC-QLQ-C30: fatigue; global health status/quality of life subscale
- SF-36v2: MCS
- EQ-5D-5L utility score and VAS

Descriptive statistics will be provided for all PRO endpoints at each time point, by treatment group. In addition, the above summaries will also be tabulated by hematologic response (responder vs. non-responder). Line plot of mean with standard error over time will be displayed by treatment group.

For the key PRO endpoints, time to worsening and time to improvement will be derived. A distribution-based method will be used to define worsening/improvement in scores, i.e., half standard deviation away from the mean score at baseline combining both treatment groups. Time to worsening/improvement will be summarized using descriptive statistics and estimated using Kaplan-Meier methods. The hazard ratio and its associated 95% confidence interval (CI) will be calculated based on the stratified Cox proportional hazards model by the stratification factor at randomization. Death due to disease progression will be considered as worsening. Subjects who have not met the definition of worsening will be censored at the last PRO assessment. Subjects without baseline assessment or post-baseline assessment will be censored at date of randomization.

A mixed effects model with repeated measures analysis will be conducted estimating change from baseline at each time point up to Cycle 6 (Week 24) between two treatments. ITT subjects who have a baseline value and at least one post-baseline value are included in the analysis. Change from baseline will be fitted to a mixed effects model including subjects as a random effect, and baseline value, treatment group, time in week, treatment-by-time interaction, and stratification factors as fixed effects.

Other PRO endpoints

These include other EORTC-QLQ-C30 scales and single items:

- functional scales: physical, role, cognitive, emotional, and social
- multi-item symptom scales: pain, nausea and vomiting
- single-item symptom scale: dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties
- additional single items to EORTC-QLQ-C30: swelling in legs or ankles, bloated feeling in abdomen/stomach, tingling hands or feet, dizzy

SF-36vs scales:

- physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health
- physical component summary (PCS)

The change from baseline at each time point will be summarized descriptively by treatment group. Line plot of mean with standard error over time may be displayed by treatment group.

Time to worsening/improvement and mixed effect model analysis, as described for the key PRO endpoints, may be performed as appropriate.

5.6. Subgroup Analysis of Efficacy Endpoints

Subgroup analysis of the primary endpoint CHR, major secondary endpoints of MOD-PFS and OS based on pre-specified subgroups defined in Section 2.12 will be conducted to investigate the consistency of the treatment effect across subgroups.

6. SAFETY

Safety assessment will be evaluated through AEs, clinical hematology and chemistry laboratory tests, ECGs, Transthoracic Echocardiogram (TTE), vital sign measurements, physical examination findings, and ECOG performance status. Safety analyses will be based on the safety population and presented by the treatment received.

6.1. Adverse Events

All adverse events whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of study treatment, until the subject withdraws consent for study participation, or until the subject starts subsequent anti-plasma cell therapy, whichever occurs first. AEs will be recorded in standard medical terminology and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. For AE reporting, the verbatim term used in the CRF by investigators to identify adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

Unless otherwise specified, at each level (e.g., system organ class and/or preferred term) of subject summarization in reporting the incidence of the AE, a subject is counted once if one or more events were recorded. For summarizing new onset events, all event records of the same preferred term from the same subject are to be linked by the onset date and the end date. If an event is followed by another event of the same preferred term with an onset date (or date/time) the same as or 1 day (or 1 minute if applicable) after the end date (or date/time) of the previous record and any features of the adverse event (i.e.: toxicity grades/seriousness/action taken) are different between these two records, these 2 records should be linked together and considered as 1 event.

All summaries of AEs will be based on treatment-emergent adverse events (TEAEs). TEAEs are defined as any AE that occurs after start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent anticancer therapy, whichever is earlier; or any AE that is considered drug-related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug-related by the investigator.

The incidence of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term, by toxicity grade, and by relationship to study treatment administration. No toxicity grade or AE relationship will be imputed when missing. Specifically, the following AE summaries will be presented by treatment group:

6.1.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each treatment group. The overview will include summaries of subjects with TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, SAEs, TEAEs leading to discontinuation of any study treatment.

A similar overview of TEAEs (new onsets) will be presented by treatment cycle.

6.1.2. All TEAEs

- Incidence of TEAEs by MedDRA SOC and preferred term
- Most commonly reported (>10%) TEAE by MedDRA SOC and preferred term
- Most commonly reported (>10%) TEAE by MedDRA preferred term

A similar summary of incidence of TEAEs by MedDRA SOC and preferred term will be presented by treatment cycle.

6.1.3. Toxicity Grade 3 or 4 TEAEs

- Incidence of toxicity grade 3 or 4 TEAEs, by MedDRA SOC and preferred term
- List of subjects with any toxicity grade 3 or 4 TEAEs
- Most commonly reported (>5%) grade 3 or 4 TEAE by MedDRA SOC and preferred term
- Most commonly reported (>5%) grade 3 or 4 TEAE by MedDRA preferred term

A similar summary of incidence of toxicity grade 3 or 4 will be presented by treatment cycle.

6.1.4. Study Treatment-Related TEAEs

- Incidence of TEAEs considered by the investigator to be related to study treatment, by MedDRA SOC, preferred term and relationship to study treatment
- Incidence of TEAEs with toxicity grade 3 or 4 considered by the investigator to be related to study treatment, by MedDRA SOC and preferred term and relationship to study treatment

6.1.5. Serious Adverse Events (SAEs)

- Incidence of treatment-emergent SAEs, by MedDRA SOC and preferred term
- Incidence of treatment-emergent SAEs considered by the investigator to be related to study treatment, by MedDRA SOC, preferred term and relationship to treatment
- List of subjects with any treatment-emergent SAEs

A similar summary will be presented by treatment cycle.

6.1.6. TEAEs Leading to Cycle Delays or Dose Modifications

Incidence of TEAEs leading to treatment cycle delays or dose modifications will be summarized by MedDRA SOC and preferred term. The summaries will be presented by all grades and grade 3 or 4 for each treatment. This table will include TEAEs leading to cycle delays or at least 1 of study treatments dose modifications, the dose modifications include dose delays, dose skipping, or dose reduction (applicable to cyclophosphamide, bortezomib and dexamethasone).

6.1.7. TEAEs Leading to Discontinuation of Any Study Treatment

A summary of number of subjects who discontinued any study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred term will be provided. The summaries will be presented by all grades and grade 3 or 4 for each treatment group. The AEs leading to discontinuation of any study treatment are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study treatment.

A list of subjects who discontinued any study treatment will be provided.

6.1.8. TEAEs Leading to Discontinuation of Study Treatment

A summary of number of subjects who discontinued study treatment because of 1 or more TEAEs by MedDRA system-organ class and preferred Term will be provided. The summaries will be presented by all grades and grade 3 or 4 for each treatment group. This table includes AEs leading to discontinuation of all study treatment for those subjects indicated as having discontinued study treatment due to an adverse event on the end of treatment CRF page.

6.2. Deaths**6.2.1. All Deaths**

A summary of all deaths and cause of death will be tabulated overall and by treatment group. Specifically, the number of subjects who died during the study will be summarized for the ITT population. The primary cause of death collected on CRF page will be reported. If the primary cause of death reported is a TEAE, the number of subjects who have a treatment related AE and unrelated AE will be further reported. Similar summaries will be presented for subjects who died within 30 days of last study treatment dose and within 60 days of first study treatment dose, respectively.

A listing of subjects who died during the study will be provided.

6.2.2. Death Due to TEAEs

The number of subjects who died due to treatment-emergent adverse events will be summarized by preferred term and relationship to study treatment for each treatment group. The TEAEs included in this table are AEs with outcome death or toxicity grade 5 recorded in the AE CRF page.

A listing of subjects who died due to treatment-emergent adverse events will be provided.

6.3. Adverse Events of Clinical Interest**6.3.1. Infusion-Related Reactions (IRR)**

Subjects with any IRR associated with daratumumab administration will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades, grade 3, 4, and 5. In addition, the total number of subjects with IRR in more than 1 infusion will

be reported. Additionally, the timing of IRR associated with daratumumab administration will be evaluated through a summary of IRR by event onset time.

A listing of subjects with grade 3 or higher treatment-emergent infusion-related reactions associated with daratumumab administration will be provided. In addition, subjects with treatment-emergent infusion-related reactions results in discontinuation of daratumumab will be listed.

6.3.2. Local Injection Site Reactions (LISR)

Subjects with any local injection site reaction associated with daratumumab administration will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades, grade 3, 4, and 5. In addition, the total number of subjects with IRSR in more than 1 infusion will be reported. Additionally, the timing of IRSR associated with daratumumab administration will be evaluated through a summary of IRSR by event onset time.

A listing of subjects with grade 3 or higher treatment-emergent IRSR associated with daratumumab administration will be provided. In addition, subjects with treatment-emergent IRSR resulting in discontinuation of daratumumab will be listed.

6.3.3. Infections and Infestations

Infections and infestations refer to adverse events with Body System/Organ Class of infections and infestations. A summary of number of subjects with 1 or more toxicity grade 3 or 4 treatment-emergent infections and infestations by MedDRA preferred term and relationship to treatment will be provided. In addition, incidences of grade 3 or 4 treatment-emergent infections and infestation will be summarized by MedDRA preferred term and treatment cycle.

Time to first onset of infections/infestations event may be explored.

6.3.4. Herpes Zoster Reactivation

The incidence of all and grade 3 or 4 herpes zoster reactivation events will be presented by MedDRA higher level term and preferred term for each treatment group.

6.3.5. Hepatitis B Virus Reactivation

Reactivation of hepatitis B refers to the abrupt increase in hepatitis B virus (HBV) replication in a subject with inactive or resolved hepatitis B. The number of subjects with HBV history and incidence of HBV reaction events will be descriptive summarized, if applicable.

A list of subjects with HBs (HB virus core antibody, HB virus surface antibody, HB virus surface antigen, and HBV viral load) test will be provided for safety population.

6.3.6. Peripheral Neuropathies

Peripheral neuropathies (PNs) refer to adverse events with high level term (HLT) of peripheral neuropathies NEC. Incidences of PNs will be summarized by MedDRA high level term and

preferred term. The summaries will be presented by all grades and grade 3 or 4 for each treatment group.

6.3.7. Cardiac Disorders

Incidences of all grades and grade 3 or 4 treatment-emergent cardiac disorders by MedDRA high level term and preferred term will be provided for each treatment group. Cardiac disorders refer to adverse events with Body System/Organ Class of cardiac disorders.

6.3.8. Renal and Urinary Disorders

Incidences of all grades and grade 3 or 4 treatment-emergent renal and urinary disorders by MedDRA high level term and preferred term will be provided for each treatment group. Renal and urinary disorders refer to adverse events with Body System/Organ Class of renal and urinary disorders.

6.3.9. Hepatobiliary Disorders

Incidences of all grades and grade 3 or 4 treatment-emergent hepatobiliary disorders by MedDRA high level term and preferred term will be provided for each treatment group. Hepatobiliary disorders refer to adverse events with Body System/Organ Class of hepatobiliary disorders.

6.3.10. Hemorrhage Events

Hemorrhage events refer to the adverse events defined by Standardized MedDRA Queries (SMQ) with the first subcategory SMQ of hemorrhage terms (exclude laboratory terms). Incidences will be summarized by MedDRA system-organ class and preferred term. The summaries will be presented by all grades and maximum toxicity grade for each treatment group.

6.3.11. Second Primary Malignancies

A listing of subjects who reported second primary malignancies during the study will be provided. This listing will include diagnosis, study day of diagnosis, recurrence of a prior existing malignancy (yes, no) and pathology diagnosis (biopsy, aspirate etc.) etc. information whenever a second primary malignancy is observed. In addition, cumulative study treatment exposure, and whether subjects received subsequent anticancer therapy (yes, no) information will also be presented in the listing.

6.4. Adverse Events by Subgroups

The following subgroup analysis of adverse events will be performed based on subgroups specified in Section [2.12](#).

- Overview of TEAEs
- All TEAEs
- Toxicity grade 3 or 4 TEAEs
- SAEs

6.5. Clinical Laboratory Tests

Descriptive statistics (mean, standard deviation, median, range) will be used to summarize observed laboratory values and change from baseline in observed value at each scheduled visit for each treatment group. Line plot of mean with standard error for each laboratory analyte over time will be displayed by treatment group. The laboratory analyte to be analyzed includes:

- Hematology panel: hemoglobin, WBC, platelet count, neutrophils and lymphocytes
- Chemistry panel: sodium, potassium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, and creatinine
- Cardiac biomarker: NT-proBNP, troponin and high sensitivity troponin

The worst toxicity grade in hematology and chemistry during the treatment will be summarized by treatment group and toxicity grade. Shift tables from baseline to worst toxicity grade during the treatment will be provided for each laboratory analyte listed above. These tables will summarize the number of subjects with each baseline CTC grade and changes to the maximum CTC grade.

6.6. Vital Signs and Physical Examination Findings

Temperature and blood pressure measurements at each scheduled treatment administration day will be summarized by descriptive statistics. In addition, change from baseline in each vital sign will be summarized at each measured visit.

Similar analyses will be performed for weight at each scheduled treatment administration day.

Post-baseline physical examination findings were collected as AEs, and therefore will not be summarized.

6.7. Transthoracic Echocardiogram (TTE) or Other Assessment of Cardiac Function

Echocardiogram will be performed at screening visit, Cycle 7 Day 1 and when clinically indicated, and the End-of-Treatment (if before Cycle 7 Day 1) visit. Any changes from baseline TTE measurements (specifically, changes in LVEF and changes in diastolic function) will be summarized by treatment group. Descriptive statistics will be calculated for observed values at baseline and change from baseline at each scheduled time point.

6.8. Electrocardiogram

Electrocardiogram will be collected at screening visit and the End-of-Treatment visit.

The number and percentage of subjects with normal or abnormal (clinically significant or clinically insignificant) 12-lead ECG results will be summarized.

6.9. Other Safety Parameters

6.9.1. ECOG Performance Score

ECOG performance status, which evaluates the effect of the disease status on the activities of daily living, will be assessed. Descriptive statistics will be used to summarize ECOG performance status at each measured visit for each treatment group. Meanwhile, shift table from baseline to each post baseline visit and to worst ECOG performance score will be provided.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Unless specified otherwise, descriptive statistics (e.g., number of observations, mean, standard deviation, median, and range) will be used to summarize pharmacokinetics and pharmacodynamics data. In addition, coefficient variation and geometric mean will be provided in the pharmacokinetic concentration summary.

7.1. Pharmacokinetics

7.1.1. Sampling Timepoints

For subjects assigned to Dara SC+CyBorD, blood samples to assess serum concentration (pharmacokinetics) of daratumumab will be obtained at Cycle 1 Day 1, Day 4 (± 1 day), Day 8, Cycle 2 Day 1, Cycle 3 Day 1, Day 4 (± 1 day), Cycle 7 Day 1, Cycle 12 Day 1, End-of-Treatment (Post-Treatment Week 4) and Post-Treatment Week 8. On a daratumumab dosing day, blood samples need to be collected before (up to 2 hours but not after the start of infusion) and immediately after (up to 2 hours but not before the end of infusion) daratumumab administration.

7.1.2. Pharmacokinetic Parameters

The pharmacokinetic parameters are defined as:

- Minimum observed concentration (C_{\min}) - the concentration observed immediately before infusion.
- Maximum observed concentration (C_{\max}) – the concentration observed after the end of infusion

For daratumumab, the pharmacokinetic evaluations include C_{\min} and C_{\max} . If sufficient data are available, then other pharmacokinetic parameters may be calculated.

7.1.3. Analysis Methods

Pharmacokinetic analyses will be performed on the pharmacokinetic-evaluable population. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics will be used to summarize daratumumab serum concentrations at each sampling time point specified in Section 7.1.1. Line plot of mean (\pm SD) daratumumab serum concentrations over time will be provided.

The C_{\max} and C_{\min} will be determined based on visual inspection of the serum concentration data. If sufficient data are available, population pharmacokinetic analysis of serum concentration-time data of daratumumab may be performed using nonlinear mixed-effects modeling. If population pharmacokinetic analysis is conducted, it may include data from other clinical studies; details will be provided in a population pharmacokinetic analysis plan and results will be presented in a separate report.

7.2. Immunogenicity

7.2.1. Sampling Timepoints

Samples to assess the generation of antibodies to daratumumab (immunogenicity)/ rHuPh20 will be obtained from all subjects in the Dara SC+CyBorD arm at Day 1 predose of Cycle 1, 2, 3, 7 12, End-of-Treatment (Post-Treatment Week 4) and 8 weeks after last dose of dara (Post-Treatment Week 8). When an IRR occurs associated with the second daratumumab administration or beyond, 2 separate blood samples should be obtained, if possible, for determination of antibodies to daratumumab and antibodies to rHuPH20. No unscheduled samples need to be collected for infusion reactions associated with the first infusion of daratumumab.

7.2.2. Analysis Methods

The incidence of antibodies to daratumumab (immunogenicity)/ rHuPh20 will be summarized for all subjects who receive a dose of daratumumab and have appropriate samples for detection of antibodies to daratumumab/ rHuPh20. In addition, subjects who are positive for antibodies to daratumumab/ rHuPh20 will also be listed.

7.3. Pharmacokinetic/Pharmacodynamic Analyses

If sufficient data are available, other pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of daratumumab and endpoints of clinical efficacy. If analysis is conducted, details and results of the analysis will be presented in a separate report.

8. BIOMARKER

Biomarker studies are designed to identify markers predictive of response (or resistance) to daratumumab. Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging study data show no likelihood of providing useful scientific information. Results of biomarker analyses may be presented in a separate report.

Biomarker evaluations in this study will focus on the evaluation of CD38 expression by IHC on the malignant plasma cells from core diagnostic biopsies to determine if CD38 expression correlates with response to daratumumab. Bone marrow aspirate will also be obtained to evaluate minimal residual disease (MRD). Minimal residual disease may be monitored in subjects who achieve CHR using next generation sequencing (NGS) or similar technologies which utilize malignant plasma cell DNA from bone marrow aspirates.

As MRD was an exploratory objective without a mandatory sample collected, the MRD analysis will be based on MRD evaluable subset, which is defined as subjects who have both baseline and post-baseline MRD (with negative, positive or indeterminate result) samples taken.

Descriptive statistics for values and changes from baseline at each scheduled visit for PD biomarkers such as T cells, CD38+ MDSCs and Tregs will be provided. Box plots of T cells, CD38+ MDSCs and Tregs over time will be presented.

Exploratory analysis may be conducted to explore minimal residual disease status in AL amyloidosis patients as a surrogate for PFS and OS or as a biomarker for relapse.

9. PHARMACOGENOMIC ANALYSES

Bone marrow aspirate from subjects in both treatment groups will be used for pharmacogenomic evaluation to allow the identification of genetic factors that may influence the pharmacodynamics, efficacy, safety, or tolerability of daratumumab.

Pharmacogenomic analysis results will be presented in a separate report.

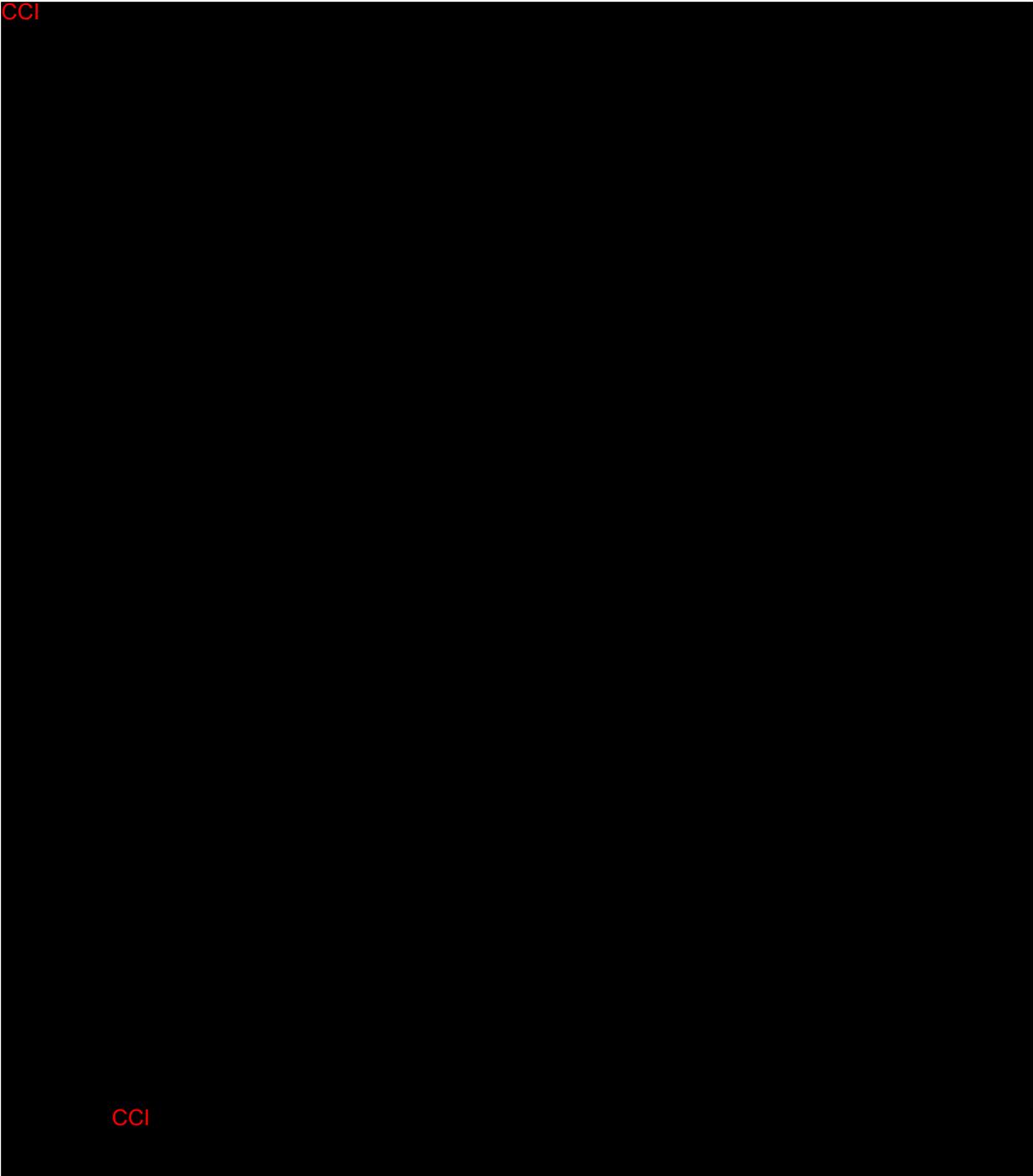
10. MEDICAL RESOURCE UTILIZATION

Medical resource utilization will be descriptively summarized by treatment group. Frequencies of hospitalization, outpatient visits, type of hospitalization or outpatient visit, reasons for hospitalization or outpatient visit, durations of hospitalization or outpatient visit, types of adverse events if involved, blood product transfusions, antibiotic use, and other concomitant medication will be calculated and tabulated.

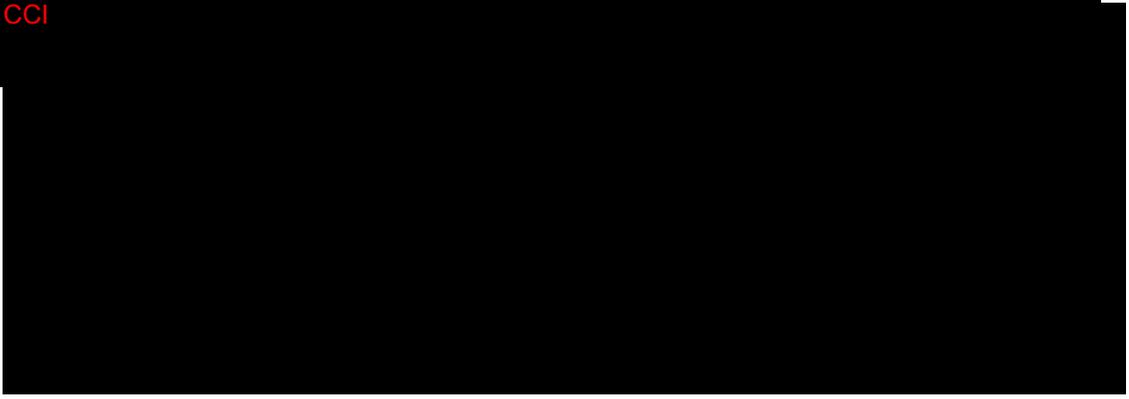
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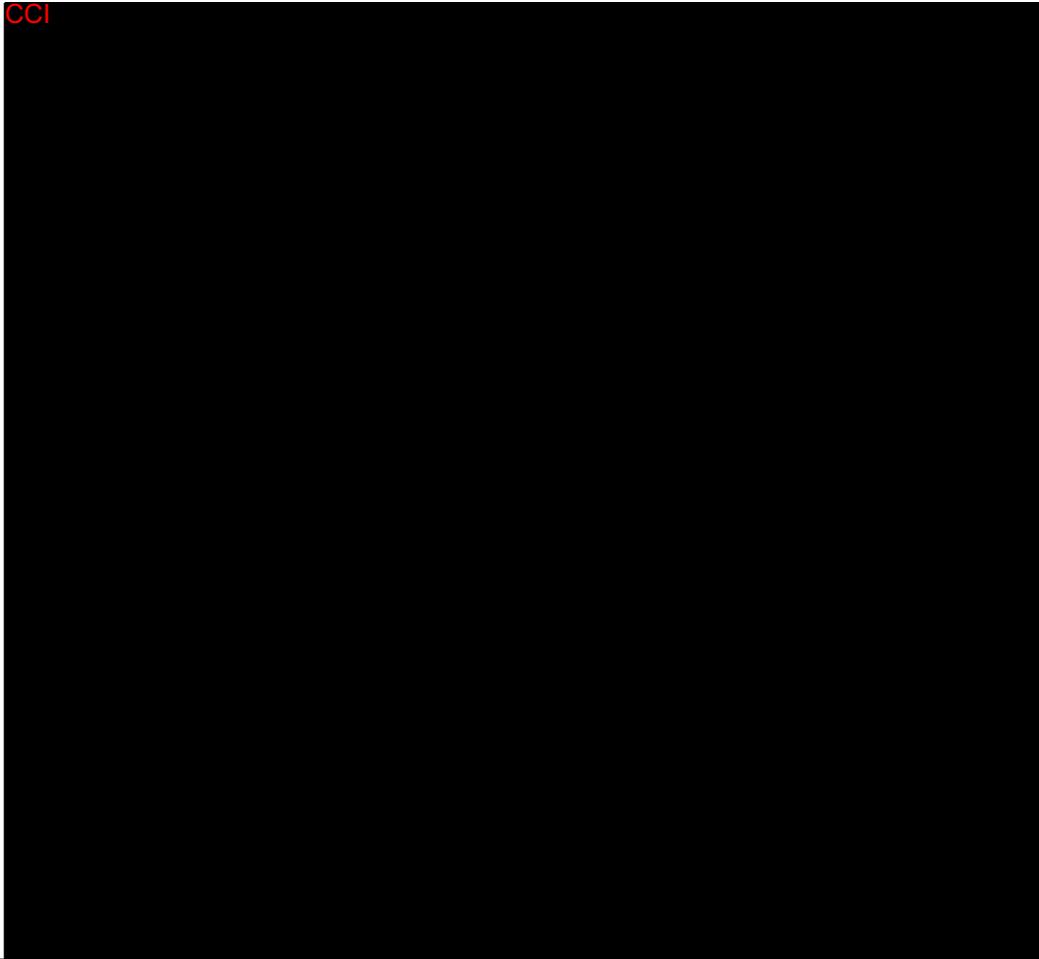
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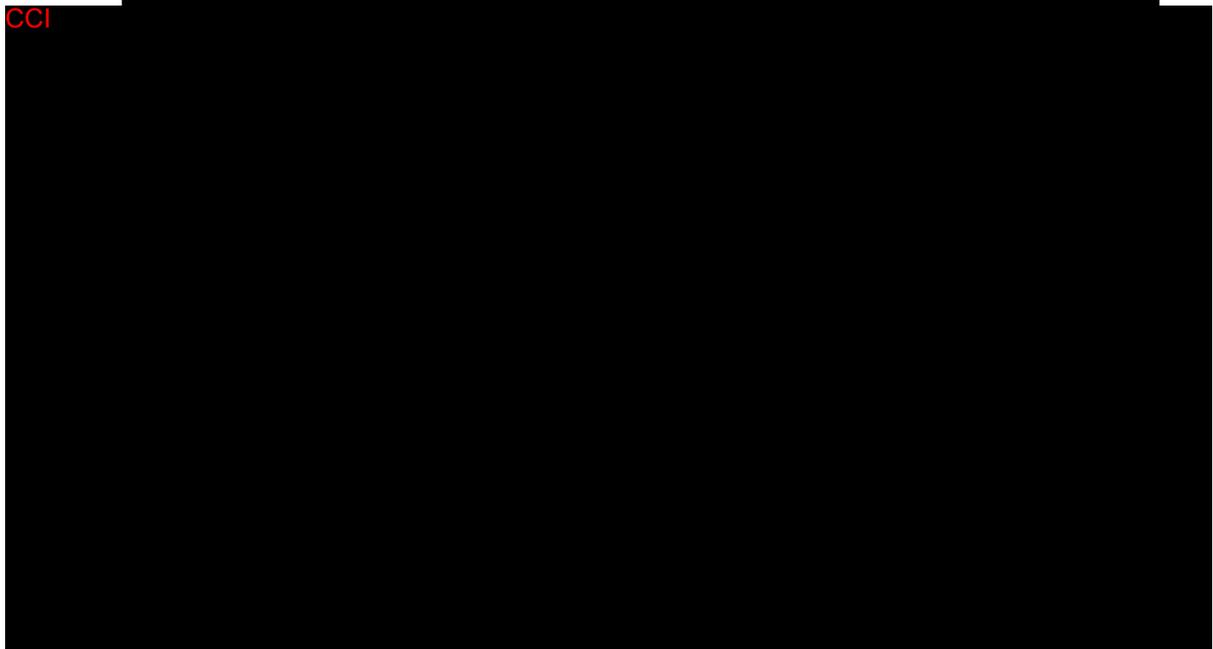
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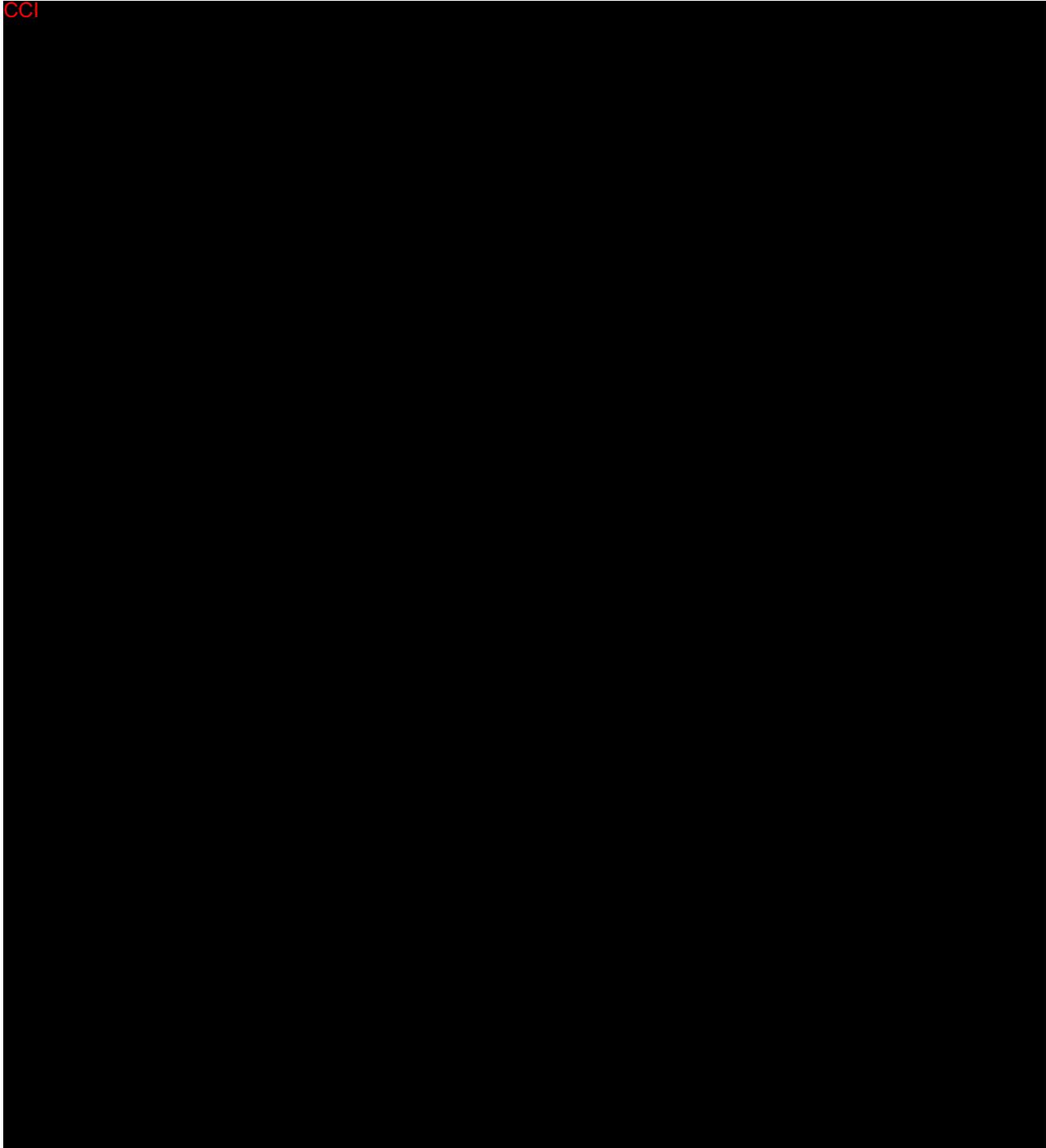
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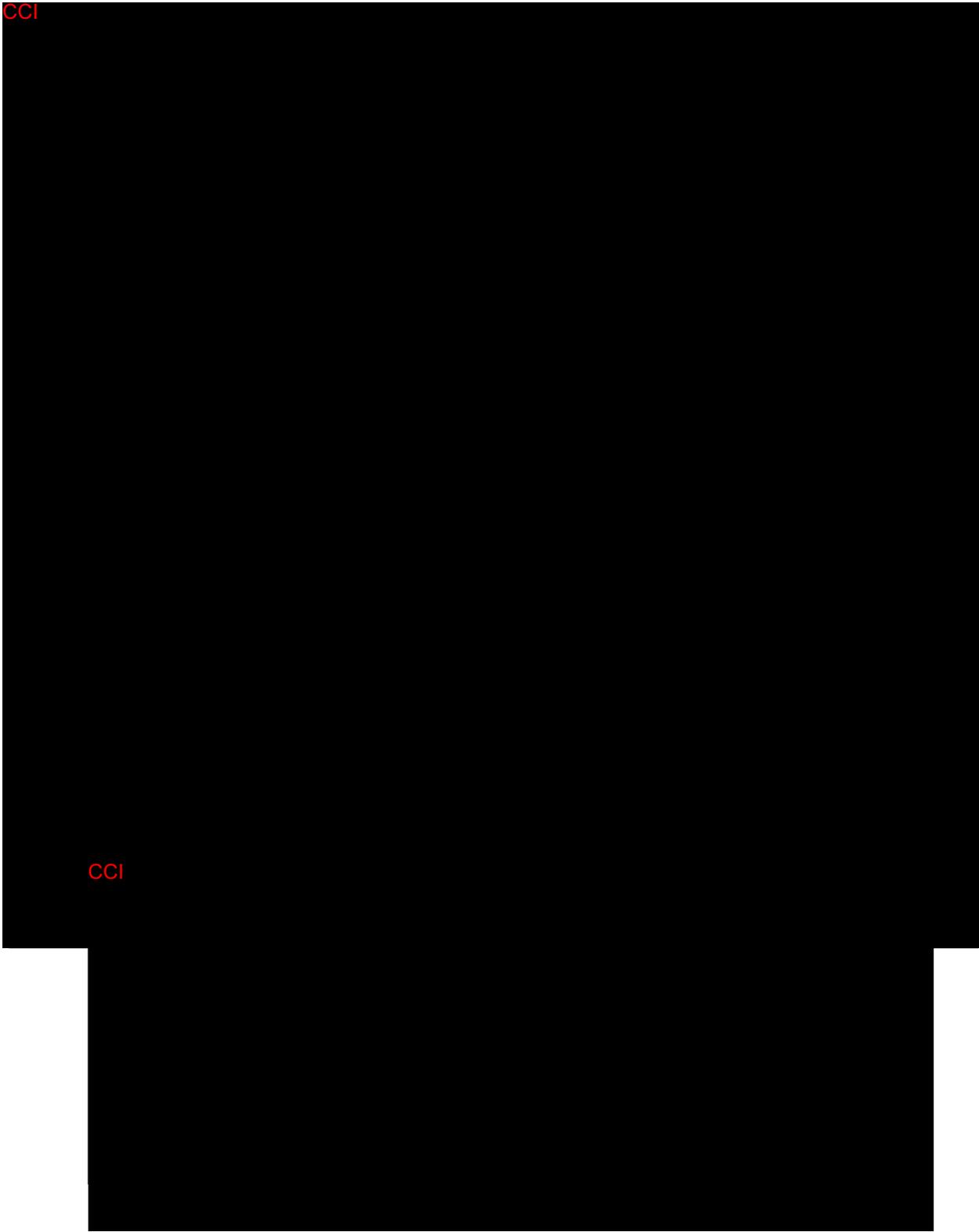
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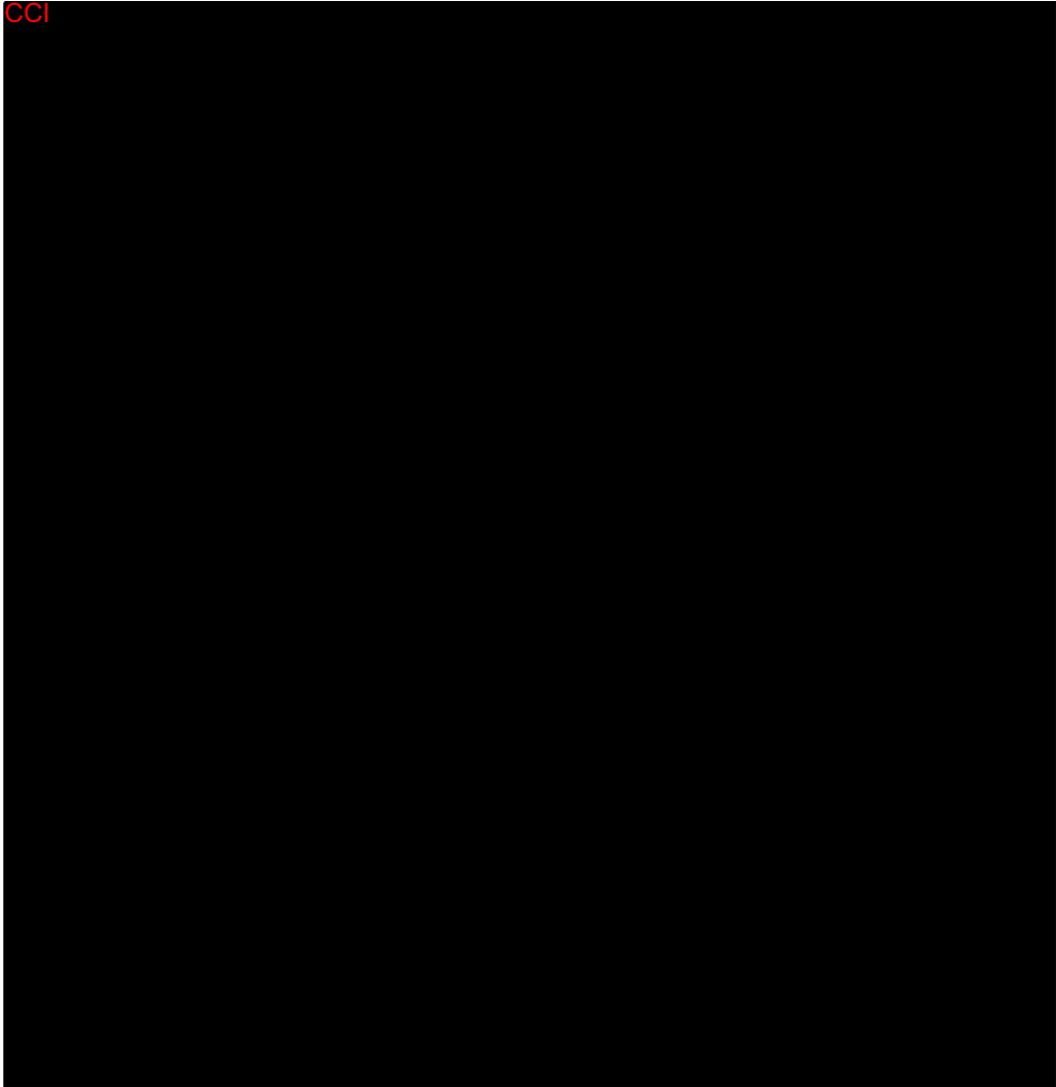


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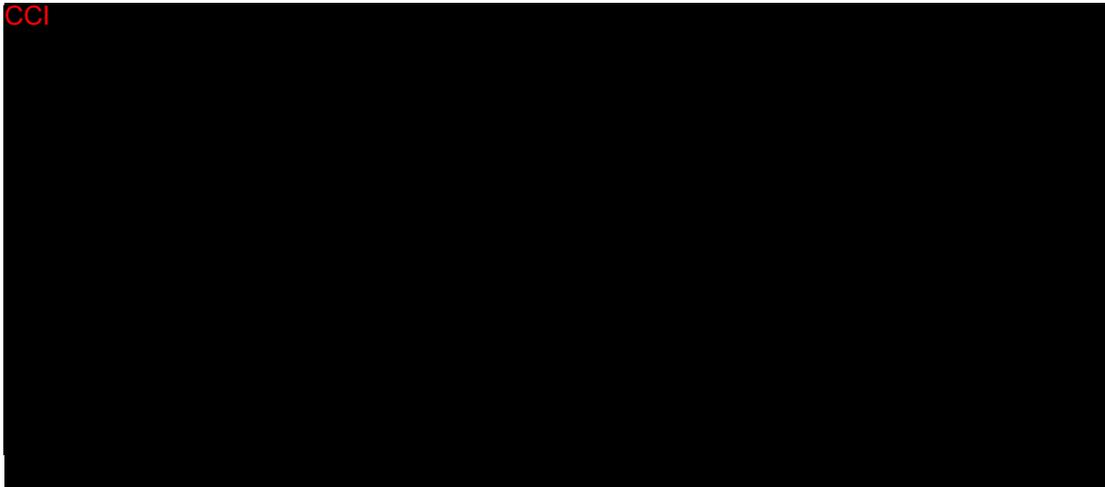


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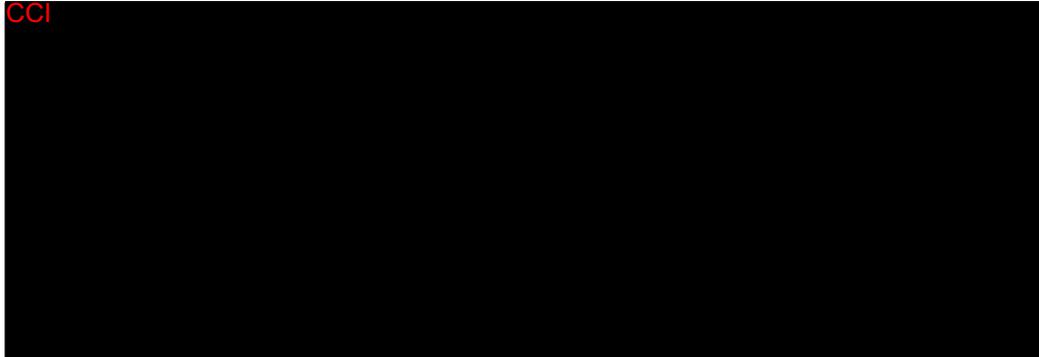
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ATTACHMENT 2: GUIDELINES FOR SUBSEQUENT THERAPY**Guidelines for Subsequent Therapy**

Response after six cycles of initial therapy	Action taken
Hematologic Response (PR or better) with stable/improved major organ function	Observation or daratumumab monotherapy until disease progression
Hematologic Response (PR or better) with worsening major organ function	Subsequent therapy may be considered
Hematologic Non-Response or disease progression with stable/improved organ function	Subsequent therapy may be considered
Hematologic Non-Response or disease progression with worsening organ function	Subsequent therapy recommended

**ATTACHMENT 3: COUNTRIES THAT TYPICALLY OFFER STEM CELL
TRANSPLANT: LIST A OR LIST B**

List A (Patients typically offered transplant)

Australia
Brazil
Canada
Germany
Hungary
Italy
Japan
The Netherlands
Poland
Romania
S. Korea
Spain
Sweden
Turkey
UK
US

List B (Patients Not typically offered transplant)

Belgium
China
Denmark
France
Greece
Israel
Mexico

ATTACHMENT 4: INDEPENDENT REVIEW COMMITTEE**Independent Review Committee**

The independent review committee (IRC) will be composed of three physicians with expertise and clinical experience in the diagnosis and management of AL Amyloidosis. However, they will not have direct involvement in the conduct of the study. The IRC members will perform an independent review of data from all randomized subjects. The primary purpose of the IRC review will be to provide an independent determination of PD (hematologic and organ progression, respectively) and response (hematologic and organ response, respectively) and ensure consistent evaluation of PD and response for all subjects in this study.

The review performed by the IRC will be independent of the investigator's disease response assessments performed during the study. The IRC will not be provided with the identification of the study site, or treatment group. The three IRC members will be given a subject profile that includes hematologic and organ (cardiac, renal and liver) information, and a worksheet to determine and record the development of PD as well as response per visit date, confirmed hematologic response, confirmed organ response for each organ. In addition, the reason for development of PD will be recorded.

For each subject, the overall IRC-assessed response and PD and corresponding time at each disease evaluation will be determined based on a majority (2/3) quorum. For response at a disease evaluation that IRC has a different assessment, every effort will be taken to resolve any difference among 3 IRC members, and ensure at least 2 IRC members to have the same response evaluation. if there is no resolution, the IRC chair will decide.

ATTACHMENT 5: ADDITIONAL EXPLORATORY ANALYSIS TO SUPPORT HEMAR

1. DEFINITION OF SUBGROUPS

Subgroup analyses will be performed using the criteria listed below to determine whether the treatment effect is consistent among subgroups. Analyses will be conducted for the ITT population and for the following subgroups:

- For subjects who received transplant as subsequent therapy
- For subjects who achieve CRR
- For subjects who achieve RRR
- For subjects who achieve LRR
- For subjects who reached CHR as their best response
- For subjects who reached VGPR as their best response
- For subjects who had baseline ECOG of 1
- For subjects who had baseline ECOG of 2
- For subjects who achieved MRD negativity (10^{-4} , 10^{-5} and 10^{-6})

Subgroup analyses will be performed if data warrants.

2. TIME-TO-EVENT ENDPOINTS FOR SUBGROUP ANALYZES

Kaplan-Meier estimates will be used to estimate distribution of time to event by treatment group based on all ITT population. Data will be calculated and summarized with descriptive statistics. The following time-to-event endpoints will be analyzed by pre-defined subgroups as defined in section 2.12 and in section 1 above:

- MOD-PFS
- HemPFS
- OS

2.1. Subgroup Analysis by Center for CHR Rate, MOD-PFS, HemPFS, OS and EQ-5D and EORTC QLQ C30

3. EXPOSURE ADJUSTED INCIDENCE RATES (EAIR)

3.1. Restriction on the first event

The analysis restricts on the occurrence of the first event per patient and ignores the existence of later (multiple) events as these cannot be assumed to occur independent of previous events (e.g.: patients suffering from infections may have in general a higher risk of having other complications and may even have a higher risk of getting other infections). The occurrence of multiple events is subject to another analysis considering the absolute number of adverse events per patient.

For these reasons the EAIR should be interpreted as *'rate until the first event occurs'*. Rates estimated from several patients can be averaged on the level of a preferred term (PT), of a system organ class (SOC), or on a global level (see below).

The interpretation of EAIRs is simple and consistent on the preferred-term level only, and can be expressed as *"Average number of TEAEs per preferred-term emerging per person-month of exposure"*.

The aforementioned considerations apply in the same way to EAIRs estimated on the global level: when EAIRs are collapsed into the global estimate (first analyses), the estimate can be interpreted as the *"Average number of TEAEs emerging per person-month and PT"*, because estimation has been performed on a *'per PT'*-basis (per *average* or *typical* PT among all PTs).

Comparing EAIRs on the level of the SOC or on the global level involves data destruction because a patient's information is reduced to the first TEAE only (and possibly to a TEAE of marginal relevance among many TEAEs with higher clinical relevance).

The EAIR analysis focuses on the 'speed' by which TEAEs emerge. The analysis restricts on the first event of a patient because independence of TEAEs cannot be assumed. The necessity to restrict on the first event entails considerable data destruction when deriving SOC-specific EAIRs or the EAIR on a global level. To overcome this, the *'per PT'*-analysis, which is reported in both Tables identically, is preferable.

Comparing EAIRs between the analyses outlined below on a SOC-specific or a global level demonstrates that the *'per PT'*-method makes the interpretation of results more difficult. However, it can be suggested that this method provides a more robust approach when the two treatment groups are to be compared on a SOC-specific or global level. A t-Test like comparison of PT-specific estimates between the two treatment groups may provide a more robust, comprehensive and easy-to-communicate way of visualizing and comparing results.

3.2. Duration of exposure: censored & non-censored

The incidence rate for a patient is derived from the duration of exposure to treatment of that patient. When averaging incidence rates, a patient's duration of exposure is given either A) by the time when the event has occurred (non-censored data), or B) by the total duration of treatment in case the patient does not show the adverse event in question (censored data). Depending on whether a patient has an adverse event or not, the duration of exposure enters the denominator in its non-censored or censored form, respectively.

3.3. Incidence rate per patient

The incidence rate for a specific event of a patient i is the reciprocal of time t when the first event occurs:

$$EAIR_i = \frac{1}{t_i}.$$

3.4. Average EAIR

The $EAIR$ averaged over all patients is

$$EAIR = \frac{\sum_{i=1}^n TEAE_i}{\sum_{i=1}^n t_i},$$

whereby

- a TEAE enters the sum in the nominator unweighted ($TEAE_i = 1$, otherwise $TEAE_i = 0$), and
- the duration of exposure enters the denominator as described before: $t_i =$

$$\begin{cases} \text{time of TEAE if occurring (non-censored data)} \\ \text{total duration of treatment if no event occurs (censored data)} \end{cases}$$

3.5. EAIRs on the level of a SOC and on the global level on a 'per-PT' basis

3.5.1. Average EAIR per PT

The $EAIR$ for a specific PT is an average over all patients, i.e.

$$EAIR_{PT} = \frac{\sum_{i=1}^n TEAE_{PT,i}}{\sum_{i=1}^n t_{PT,i}},$$

whereby the number of TEAEs and durations of exposure enter the nominator and the denominator.

3.5.2. Average EAIR per SOC

The average $EAIR$ per SOC considers the first event of each patient within the SOC. The denominator includes the exposure time of each adverse event of all PTs within the SOC, per patient, i.e.

$$EAIR_{SOC} = \sum_{i=1}^n TEAE_{SOC,i} \sum_{PT=1}^{n \text{ PTs per SOC}} \frac{1}{t_{PT,i}},$$

where $TEAE_{SOC,i}$ is the first event per patient per SOC and $t_{PT,i}$ is the exposure time for a specific preferred term of a given patient.

Note: This *EAIR* is an incidence rate per *average (or typical)* preferred term in that SOC (cf. 3.6.1).

3.5.3. Average EAIR on a global level

The average *EAIR* on a global level only considers the first event per patient across all events. The denominator includes the exposure times of all PTs, i.e.

$$EAIR_{global} = \sum_{i=1}^n TEAE_i \sum_{PT=1}^n \frac{1}{t_{PT,i}},$$

where $TEAE_i$ is the first event of a patient overall and the $t_{PT,i}$'s are PT-specific exposure times of that patient.

Note: This *EAIR* is an incidence rate *per average (or typical)* preferred term.

3.6. Second analyses

3.6.1. Average EAIR per PT

The *EAIR* for a specific PT is an average over all patients as described before, i.e.

$$EAIR_{PT} = \frac{\sum_{i=1}^n TEAE_{PT,i}}{\sum_{i=1}^n t_{PT,i}},$$

whereby the number of TEAEs and durations of exposure enter the nominator and the denominator.

3.6.2. Average EAIR per SOC

The average *EAIR* per SOC considers the first event per patient per SOC only, and only one (the corresponding) exposure time in the denominator (confer before, where the denominator in the $EAIR_{SOC}$ depends on the number of PTs per SOC):

$$EAIR_{SOC} = \frac{\sum_{i=1}^n TEAE_{SOC,i}}{\sum_{i=1}^n t_{SOC,i}},$$

Note: This *EAIR* is an incidence rate *per SOC*.

3.6.3. Average EAIR on a global level

The average *EAIR* on a global level considers the overall first event per patient only, and only one (the corresponding) exposure time in the denominator (confer before, where the denominator in the $EAIR_{SOC}$ depends on the overall number of PTs):

$$EAIR_{global} = \frac{\sum_{i=1}^n TEAE_i}{\sum_{i=1}^n t_i},$$

whereby $TEAE_i$ represents the first TEAE among all TEAEs of patient i and t_i as before (time when TEAE occurs (non-censored data) or total duration of treatment if no event occurs (censored data))

4. ADDITIONAL TIME TO EVENT ANALYSES

In case of different exposure times, time adjustment for AE is necessary. Hazard Ratio and Kaplan-Meier curves will be conducted including number of patients at risk for the following safety endpoints:

- Any TEAE
- Any Serious TEAE
- Any TEAE leading to death
- Any Grade 3 or 4 TEAE
- Any Grade 3 or higher TEAE
- Any TEAE leading to treatment discontinuation

Detailed description by preferred term:

- TEAEs by preferred term with prevalence $\geq 10\%$
- Grade 3 or 4 TEAEs preferred term with prevalence $\geq 5\%$
- Grade 3 or higher TEAEs by preferred term prevalence $\geq 5\%$
- Serious TEAEs preferred term with prevalence $\geq 2\%$
- TEAEs leading to treatment discontinuation preferred term with prevalence $\geq 1\%$
- TEAE leading to death preferred term without prevalence cut-off